UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ORTHO-MCNEIL PHARMACEUTICAL, INC., ORTHO-MCNEIL, INC., and DAIICHI SANKYO CO., LTD. Plaintiffs/Counterclaim-Defendants, v. LUPIN PHARMACEUTICAL, INC. and LUPIN LTD. Defendants/Counterclaim-Plaintiffs.	Civ. Action No. 06-4999 (GEB)(TJB) Chief District Judge Garrett E. Brown, Jr. Magistrate Judge Tonianne J. Bongiovanni

DECLARATION OF DAVID T. LIN, Ph.D.

I, David T. Lin, declare as follows:

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drugs, biotechnological and biological products.

2. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I became the acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry. In 2004, I was promoted to the position of acting Division Director.

3. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. As the acting Deputy Division Director and acting Division Director of the Office of New Drug Chemistry, I directly managed and supervised chemists with review responsibilities in the following 6 medical-reviewing divisions: (1) anti-viral, (2) dermatologic/dental, (3) anti-inflammatory/analgesic/ophthalmologic, (4) anti-infective, (5) special pathogen/immunologic, and (6) over-the-counter drugs. I have reviewed CMC data submitted to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the Co-chair of the CMC Good Review Practices Committee.

4. I consider myself an expert in the fields of FDA practice and procedure as applicable to the chemical characterization of drugs and review of Investigational New Drug Applications and New Drug Applications.

5. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002.

6. My curriculum vitae is attached hereto as Exhibit A.

I. THE FDA, INVESTIGATIONAL NEW DRUG PROCESS, AND NEW DRUG APPLICATION PROCESS

A. The FDA

10. The FDA is a federal agency responsible for, among other duties, ensuring that a drug marketed in the United States is safe and effective for use as described in the labeling of the drug, and can be adequately manufactured, processed and packed to preserve the drug's identity, strength, quality and purity.[1]

11. All drugs possess critical quality attributes (specifications) that are necessary to ensure the safe and efficacious use of the product by consumers. These quality attributes are assessed during clinical trials through the use of drug product manufactured with specified performance characteristics. Some of the critical characteristics are level of impurities, source of impurities (*e.g.*, from drug substances, excipients, container closure components), foreign particulate matter, color, amount of active ingredient and breakdown products, and microbial load.

B. The Investigational New Drug Process

12. Federal law requires that all drug products be approved before marketing and administration to humans. *See* 21 USC § 355(a). When a drug product is under investigation, however, the sponsor of the application typically will need to conduct clinical trials and other investigational activities. To do so, the sponsor obtains an exemption from the federal law by filing an Investigational New Drug ("IND") application with the FDA.

[1] *See* 21 USC § 355 (d).

13. The IND is required before a sponsor can begin conducting any investigational studies that involve administration of the drug product to humans. *See* 21 CFR § 312. Prior to obtaining the IND, the sponsor will conduct pre-clinical studies in animals or non-human species to determine if the drug product is reasonably safe for use in humans and whether the drug product exhibits pharmacological activity that justifies commercial development. The IND must contain information that will allow the FDA to determine whether the drug product and study design are safe and will not subject the study participants to any unreasonable risks. In order for the FDA to make this assessment, the IND must contain information on animal pharmacology and toxicity, manufacturing, clinical protocols and clinical investigators.

14. Once the IND is in effect, the sponsor can start clinical studies. Clinical studies conducted under an IND can be segregated into three phases: Phase 1, Phase 2 and Phase 3. Phase 1 studies are intended to determine the metabolic and pharmacologic actions of the drug product, the side effects associated with increasing doses, and, if possible, signs of efficacy. Phase 2 studies are conducted on a larger number of subjects with the disease or condition to be treated. Clinical studies conducted are well-controlled and closely monitored to gather preliminary data on the drug product's effectiveness. Data are also gathered on the common short-term side effects and risks associated with the drug. If preliminary data from Phase 2 suggest the drug product's effectiveness, Phase 3 studies are initiated. Phase 3 studies are large controlled and uncontrolled trials, and can be conducted using a placebo or existing treatment comparison. The purpose of these studies is to gather additional evidence of the drug product's effectiveness and safety. This data is used to determine the drug's overall benefit-risk relationship.

Information is also gathered on the occurrence and prevalence of side effects. All these data are used to extrapolate the drug product's effectiveness and safety profile to the general population and to prepare the physician labeling (prescribing information). The labeling serves as a contract between the FDA and the sponsor that delineates what information can be used to market and promote the drug product.

C. *The New Drug Application Process*

15. There are two relevant statutory bases for the submission of a New Drug Application ("NDA") that are pertinent to this case. An NDA filed under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act ("FDCA") requires submission of the full reports of the investigations used to show that the drug product is safe and effective; the components and composition of the drug; the methods, facilities and controls used for the manufacturing, processing and packing of the drug product; and the labeling for the drug product. *See* 21 USC § 355 (1). In contrast, an application filed under Section 505(b)(2) of the FDCA does not require submission of the full reports of the investigations used to show the safety and effectiveness of the drug product. The applicant can rely on data not conducted by the applicant or where the applicant does not have right of reference to those data. *See* 21 USC § 355. However, all other submission requirements under Section 505(b)(1) must be provided. The FDA conducts the same evaluation of safety and effectiveness for a submission under Sections 505(b)(1) and 505(b)(2).

16. The FDA evaluates not only the reports of the clinical investigations, but also the non-clinical pharmacology and toxicology studies conducted in animals, human pharmacokinetic and bioavailability studies, and chemistry, manufacturing and controls

information. *See* 21 CFR § 314.50. It is this complete package of information and data that allows the FDA to determine the characterization, safety and effectiveness of the drug product, and the ability of the manufacturer to produce a consistent and quality product.

II. DRUG CHARACTERIZATION.

17. The statute governing patent term extensions defines "drug product" as the "active ingredient of … a new drug…, including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." *See* 35 U.S.C. § 156(f)(2). FDA regulations define "active ingredient" as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals." 21 CFR § 210.3(b)(7); *see also* 21 CFR § 60.3(a)(2) (same).[2]

18. As part of the CMC section of each NDA, or earlier in its IND submission, the sponsor must provide a chemical characterization of the applicable active ingredient or API, in its finished drug.[3] As part of the FDA review process, the FDA reviews and determines whether the characterization of the API is accurate.

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[2] *See also* Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, enacted in 2001 and signed on to by the FDA (defining "API" as "Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of the drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.") (attached as Exhibit B).

[3] *See* 21 CFR § 312.23(a)(7)(iv)(a) and (b); 21 CFR § 314.50(d)(1)(i) and (ii).

III. CHARACTERIZATION OF ACTIVE INGREDIENTS IN THE CONTEXT OF ENANTIOMERS AND RACEMATES

19. The FDA has had occasion to review the characterization of active ingredients in the context of enantiomers and racemates in its review of INDs and NDAs seeking approval of drugs that have racemates or enantiomers as their active ingredients. FDA practice in this regard has been in accordance with the definitions of "API" and "active ingredient" that I have quoted above.

20. To my knowledge, in each and every instance in which it has considered the question, the FDA has described a racemate as a single active ingredient, distinct from its enantiomers, and each enantiomer as a single active ingredient distinct from the other and from the racemate. I am aware of dozens of examples of the FDA's characterization of racemates and enantiomers in this way and am aware of no examples of countervailing practice. FDA's practice is evident from the labeling of the drugs and their descriptions in the FDA's publication of Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). I have attached as Exhibit C to this declaration a list of drugs containing racemic active ingredients of which I am aware, together with examples of applicable product labeling and Orange Book descriptions printed from the electronic Orange Book available on the FDA website. In each case of a racemic drug, the FDA approved labeling and the Orange Book description reflect the racemate as the active ingredient. Likewise, for enantiomeric drugs, the FDA approved labeling and the Orange Book description reflect the enantiomer as the active ingredient.

21. I am not aware of any instances where the FDA has approved a racemic product based solely on tests conducted on one or both of its individual enantiomers. I am also not aware of any instances where the FDA has approved an enantiomeric product

based solely on tests conducted on the corresponding racemate.

22. The FDA's characterization of a racemate as a single active ingredient, distinct from its enantiomers, and each enantiomer as a single active ingredient distinct from the other and from the racemate is a matter of longstanding, well-known practice. Indeed, even Lupin appears to have recognized this longstanding practice. Lupin has submitted a citizen's petition to the FDA, requesting permission to submit an application for a generic fexofenadine hydrochloride product. Fexofenadine is a racemate. As part of this petition, Lupin submitted proposed labeling for its generic fexofenadine product that characterizes the "active ingredient" in the drug as racemic fexofenadine – not one or both of its enantiomers. A copy of Lupin's proposed labeling, which is attached to this declaration at Exhibit D, also is available on the FDA's website. *See* http://www.fda.gov/ohrms/dockets/DOCKETS/06p0397/06p-0397-cp00001-02-Enclosure-01-vol1.pdf (last visited October 6, 2008). Lupin characterized the "active ingredient" on the first page of the proposed labeling under the heading "Description."

23. Importantly, had FDA decided to treat racemates as combinations of multiple active ingredients (*e.g.*, combinations of their enantiomers), instead of as distinct active ingredients, racemic products would be governed by the FDA's "combination rule," which is a regulation that the FDA has developed for the approval of drugs that contain a combination of active ingredients.[4] In short, this regulation requires the sponsor to conduct testing on each component or active ingredient individually and in combination to show the contribution of each active ingredient to the efficacy and safety of the combination product. To my knowledge, the FDA has never applied this

[4] *See, e.g.*, 21 CFR § 300.50; Guidance for Industry, Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV.

regulation to racemic drug products.

IV. FDA'S ROLE IN PATENT TERM EXTENSIONS

24. From time-to-time enters, the FDA enters into Memoranda of Understanding ("MOUs") with other federal agencies in order to cooperate on certain regulatory matters for which the FDA has particular expertise. For example, in accordance with an MOU between the FDA and the United States Patent and Trademark Office (the "PTO"), which I have attached as Exhibit E to this declaration, the PTO looks to FDA expertise in determining whether certain criteria are met before granting an application for a patent term extension. One of these criteria is whether the patented active ingredient for which marketing approval was sought from the FDA was the subject of previous approval for marketing. As the MOU explains, the PTO consults FDA on this issue because it is one that the FDA is uniquely situated to answer given the FDA's role in approval and regulation of drugs.

V. CHARACTERIZATION OF OFLOXACIN AND LEVOFLOXACIN

25. I have reviewed the relevant portions of the NDA submissions for FLOXIN® and LEVAQUIN®. In accordance with its longstanding practice, the FDA approved the NDA for FLOXIN®, accepting Ortho-McNeil and Daiichi's identification of ofloxacin as a single active ingredient, distinct from either of its enantiomers. Later, the FDA approved the NDA for LEVAQUIN® accepting Ortho-McNeil's and Daiichi's identification of levofloxacin as a single active ingredient, distinct from racemic ofloxacin. This can be seen readily from the FDA's approved labeling and Orange Book listings for those drugs, which list the active ingredient in FLOXIN® as ofloxacin and the active ingredient in LEVAQUIN® as levofloxacin. *See* Exhibits F (FLOXIN®) & G

(LEVAQUIN®).

26. Further, the FDA did not treat FLOXIN® as a combination product and did not require clinical testing of ofloxacin's individual enantiomers prior to approving FLOXIN®. The FDA did require independent clinical testing of levofloxacin prior to approving LEVAQUIN® and did not base approval of LEVAQUIN® on the ofloxacin testing. This is further support for the proposition that the FDA followed its general rule in this case and considered the racemate (ofloxacin) and its enantiomer (levofloxacin) as two distinct active ingredients.

27. Finally, as per the MOU between the two agencies, the PTO asked the FDA whether the active ingredient in LEVAQUIN® had been the subject of a prior approval for marketing. In response, the FDA confirmed that it had not been earlier approved. Importantly, that correspondence specifically noted the prior approval of FLOXIN®. This was entirely in accordance with the FDA's longstanding practice with respect to treating racemates and enantiomers as distinct active ingredients, as discussed above. I have attached the correspondence between the FDA and PTO in this regard as Exhibit H to this declaration.

* * *

I declare under penalty of perjury that the foregoing is true and correct.

24-Oct-2008
Date

David T. Lin, Ph.D.

Exhibit A

DAVID TSOCHUNG LIN
9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 13+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, peptide drugs, and protein drugs.
  - 3+ years research experience at CBER/FDA.
  - 3+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) at all stages of product development, from pre-IND through post-NDA approval.
- Review and provide advice on IND and NDA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory and scientific approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- IVT Method Validation Conference, "Challenges in Understanding Impurities and Degradants for Biological/Biotechnological Products," San Francisco, CA (Oct 2008).
- IVT Method Validation Conference, "Strategies for Setting Biological Product Specifications," San Francisco, CA (Oct 2008).
- CBI 3rd Annual Stability Programs Conference, "Complex Stability Programs for Biologics," Philadelphia, PA (Jun 2008).
- IVT Lab Compliance Conference, "Stability Testing Fundamentals and Considerations in the Current Regulatory Environment," Baltimore, MD (Apr 2008).
- R&D Direction's 5th Annual Drug Development Summit, "Looking Forward in 2008: Regulatory Priorities and Considerations," Amelia Island, FL (Feb 2008).
- 2007 AAPS Annual Meeting, "Critical Stability Evaluation of Biopharmaceuticals During Clinical Development Stages," San Diego, CA (Nov 2007).
- 2007 DIA Annual Meeting, "The Impact of FDA's Quality by Design Initiative on Biologics Development," Atlanta, GA (Jun 2007).
- Institute for International Research: Formulation and Forced Degradation Strategies for Biomolecules, "Regulatory Requirements for Successful Product Development," San Diego, CA (Mar 2007).
- International Pharmaceutical Academy: Effective Management of Stability Programs, "Stability Design Considerations for Global Regulatory Filings," Toronto, Canada (Feb 2007).
- Cambridge Healthtech Institute's PepTalk: Optimizing Protein and Antibody Therapeutics, "Regulatory Considerations for the Development of Protein Therapeutic Products," San Diego, CA (Jan 2007).
- 2006 AAPS Annual Meeting, "The Impact of FDA Initiatives on the Development of Biological Products," San Antonio, TX (Nov 2006).

- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "In-Use Testing of Biotechnological and Biologic Products," Boston, MA (Oct 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "Cost Efficient Design of Stability Studies," Boston, MA (Oct 2006).
- Institute for International Research: Chemistry Manufacturing & Controls, "Clarifying and Understanding ICH Guidance to Help Meet International Requirements for Submissions," Philadelphia, PA (July 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Cost Efficient Design of Stability Studies," San Diego, CA (June 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Stability Requirements for Global Regulatory Filings," San Diego, CA (June 2006).
- CBI Stability Programs: New Approaches to Test, Analyze and Document Data for Improved Program Design and Global Compliance, "In Use Testing of Biotechnological and Biological Products," Princeton, NJ (June 2006).
- IBC/TIDES: Oligonucleotide and Peptide Technology and Product Development, "Stability Considerations and Testing for Oligo- and Peptide-Based Therapeutics," Carlsbad, CA (May 2006).
- IBC Biopharm Manufacturing and Distribution Summit: Logistics for Biopharmaceutics, "Stability Studies to Support the Chain of Custody of Biotechnology Products," Reston, VA (Dec 2005).
- 2005 AAPS Annual Meeting: AAPS Short Course on Degradation and Stability in Small Molecule Active Pharmaceutical Ingredients/Stability Testing for Global Filings, "Stability Requirements for Global Regulatory Filings," Nashville, TN (Nov 2005).
- Therapeutic Strategies Against Neurodegenerative Conditions, "The Regulatory Product Development Process," Burlington, MA (Oct 2005).
- International Pharmaceutical Federation (FIP) Workshop: Harmonizing Clinical Trial GMP and Quality Requirements Across the EU and Beyond, "The US Investigational New Drug (IND) System," Noordwijk Zee, The Netherlands (Mar 2005).
- 2004 AAPS Annual Meeting, "Phase 2 and 3 IND CMC Guidance: FDA Perspective," Baltimore, MD (Nov 2004).
- 64th Annual World FIP Congress, "Clinical Trial Application Process – CMC: US FDA Perspective," New Orleans, LA (Sep 2004).
- AAPS Pharmaceutical Technologies 3rd Summer Conference: Optimizing the Global Clinical Trial Process, "IND Applications – FDA Perspective," Cherry Hill, NJ (Aug 2004).
- 2004 DIA Annual Meeting, "FDA Stability Guidance Update," Washington, DC (Jun 2004).
- DIA Meeting on CM&C/Regulatory and Technical Strategies, "Challenges and Opportunities in CMC Requirements for Phase 2-3," Bethesda, MD (Mar 2004).
- 2003 PDA Annual Meeting, "Draft FDA Stability Guidance," Atlanta, GA (Nov 2003).
- 2003 DIA Annual Meeting, "Product Quality of Non-clinical and Clinical Trial Materials," San Antonio, TX (Jun 2003).
- PARCS Meeting, "Managing CMC Requirements during IND," Irvine, CA (Apr 2003).
- PARCS Meeting, "Use of SUPAC Guidances during IND Development," Irvine, CA (Apr 2003).
- DIA Meeting on Global Chemistry, Manufacturing and Controls: Pre IND/CTX and IND/CTX Development Challenges, "FDA Perspective on Stability Testing during IND Development," Philadelphia, PA (Feb 2003).

PUBLICATIONS

- C. Syin, D. Parzy, F. Traincard, I. Boccaccio, M.G. Joshi, D.T. Lin, X.-M. Yang, K. Assemat, C. Doerig, and G. Langeley, "The H89 cAMP-dependent protein kinase inhibitor blocks *Plasmodium falciparum* development in infected erythrocytes," *Eur. J. Biochem. 268*, 4842 (2001).
- J.P. McDaniel, C. Syin, D.T. Lin, M.B. Joshi, S. Li, and N.D. Goldman, "Expression and characterization of a *Plasmodium falciparum* protein containing domains homologous to sarcalumenin and a tyrosine kinase substrate, eps15," *Int. J. Parasitol. 29*, 723 (1999).

- D.T. Lin, N.D. Goldman, and C. Syin, "Stage specific expression of a *Plasmodium falciparum* protein related to the eukaryotic mitogen-activated protein kinase," *Mol. Biochem. Parasitol. 78*, 67 (1995).
- M.R. Harkness, M.L. Stephens, J.H. Lobos, W.P. Flanagan, K.M. Carroll, R.J. May, G.L. Warner, P.R. Wilson, A.A. Bracco, and D.T. Lin, "A comparison of aerobic PCB biodegradation in the laboratory and in the field," *Environ. Sci. Technol.* (1996).
- M.R. Harkness, J.B. McDermott, D.A. Abramowicz, J.J. Salvo, W.P. Flanagan, M.L. Stephens, F.J. Mondello, R.J. May, J.H. Lobos, K.M. Carroll, M.J.Brennan, A.A. Bracco, K.M. Fish, G.L. Warner, P.R. Wilson, D.K. Dietrich, D.T. Lin, C.B. Morgan, and W.L. Gately, "*In situ* stimulation of aerobic PCB biodegradation in Hudson River sediments," *Science 259*, 503 (1993).
- D.T. Lin, V.M. Powers, L.J. Reynolds, C.P. Whitman, G.L. Kenyon and J.W. Kozarich, "Evidence for the generation of α-carboxy-α-hydroxy-*p*-xylylene from *p*-(bromomethyl)mandelate by mandelate racemase," *J. Am. Chem. Soc. 110*, 323 (1988).
- M.S. Lakshmikumaran, E. D'Ambrosio, L.A. Laimins, D.T. Lin and A.V. Furano, "Long interspersed repeat DNA(LINE) causes polymorphism at the rat insulin 1 locus," *Mol. Cell. Biol. 5*, 2197 (1985).

BOOK CHAPTER

- N.R. Schmuff and D.T. Lin, “Chemistry, Manufacturing and Controls (CMC),” in Wiley Encyclopedia of Clinical Trials, (2007), under review.
- J.A. Gerlt, G.L. Kenyon, J.W. Kozarich, D.T. Lin, D.C. Neidhart, G.A. Petsko, V.M. Powers, S.C. Ransom and A.Y. Tsou, "Structure-function relationships in mandelate racemase and muconate lactonizing enzyme," in Chemical Aspects of Enzyme Biotechnology, T.O. Baldwin, F.M. Raushel and A.I. Scott (eds.), Plenum, New York, NY, 9-21 (1990).

PROCEEDINGS OF MEETINGS

- D.T. Lin, N.D. Goldman, and C. Syin, "*Plasmodium falciparum* mitogen-activated protein kinase homologue contains an unusually large carboxyl terminal domain which is highly charged and homologous to merozoite surface antigens," Molecular Parasitology Meeting, Woods Hole, MA (1995).
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Exhibit B

Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
August 2001
ICH

Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Additional copies are available from:

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Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
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U.S. Department of Health and Human Services
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Table Of Contents

Guidance for Industry[1]
Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

I. INTRODUCTION (1)

A. Objective (1.1)

This document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess.

In this guidance, the term *manufacturing* is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In this guidance, the term *should* identifies recommendations that, when followed, will ensure compliance with CGMPs. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes. For the purposes of this guidance, the terms *current good manufacturing practices* and *good manufacturing practices* are equivalent.

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[1] This guidance was developed within the Expert Working Group (Q7A) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2000. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Arabic numbers in subheadings reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2000.

The guidance as a whole does not cover safety aspects for the personnel engaged in manufacturing, nor aspects related to protecting the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guidance is not intended to define registration and/or filing requirements or modify pharmacopoeial requirements. This guidance does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents should be met.

B. Regulatory Applicability (1.2)

Within the world community, materials may vary as to their legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this guidance.

C. Scope (1.3)

This guidance applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidances for drug (medicinal) products as defined by local authorities.

This guidance covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section XVIII (18).

This guidance excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guidance. In addition, the guidance does not apply to medical gases, bulk-packaged drug (medicinal) products (e.g., tablets or capsules in bulk containers), or radiopharmaceuticals.

Section XIX (19) contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An *API starting material* is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material

purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which API starting materials are entered into the process. For other processes (e.g., fermentation, extraction, purification), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API starting material is normally introduced into the process.

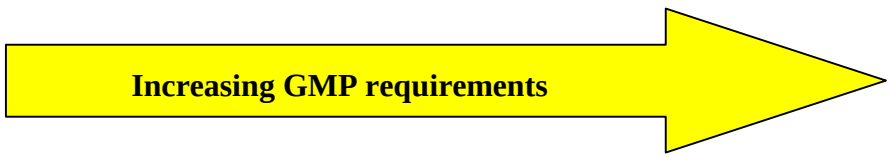
From this point on, appropriate GMP as defined in this guidance should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. However, all steps shown may not need to be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g., milling, micronizing) should be conducted according to this guidance.

This GMP guidance does not apply to steps prior to the introduction of the defined API starting material.

Table 1: Application of this Guidance to API Manufacturing

Type of Manufacturing	**Application of this guidance to steps (shown in gray) used in this type of manufacturing**				
Chemical Manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establish-ment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establish-ment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



II. QUALITY MANAGEMENT (2)

A. Principles (2.1)

Quality should be the responsibility of all persons involved in manufacturing.

Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

There should be a quality unit(s) that is independent of production and that fulfills both quality assurance *(QA)* and quality control *(QC)* responsibilities. The quality unit can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

The persons authorized to release intermediates and APIs should be specified.

All quality-related activities should be recorded at the time they are performed.

Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in Section X (10) or the use of raw materials or intermediates pending completion of evaluation).

Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality-related complaints, recalls, and regulatory actions).

B. Responsibilities of the Quality Unit(s) (2.2)

The quality unit(s) should be involved in all quality-related matters.

The quality unit(s) should review and approve all appropriate quality-related documents.

The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include, but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company

2. Establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials

3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution

4. Making sure that critical deviations are investigated and resolved

5. Approving all specifications and master production instructions

6. Approving all procedures affecting the quality of intermediates or APIs

7. Making sure that internal audits (self-inspections) are performed

8. Approving intermediate and API contract manufacturers

9. Approving changes that potentially affect intermediate or API quality

10. Reviewing and approving validation protocols and reports

11. Making sure that quality-related complaints are investigated and resolved

12. Making sure that effective systems are used for maintaining and calibrating critical equipment

13. Making sure that materials are appropriately tested and the results are reported

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates, where appropriate

15. Performing product quality reviews (as defined in Section 2.5)

C. Responsibility for Production Activities (2.3)

The responsibility for production activities should be described in writing and should include, but not necessarily be limited to:

1. Preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures

2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions

3. Reviewing all production batch records and ensuring that these are completed and signed

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded

5. Making sure that production facilities are clean and, when appropriate, disinfected

6. Making sure that the necessary calibrations are performed and records kept

7. Making sure that the premises and equipment are maintained and records kept

8. Making sure that validation protocols and reports are reviewed and approved

9. Evaluating proposed changes in product, process or equipment

10. Making sure that new and, when appropriate, modified facilities and equipment are qualified

D. Internal Audits (Self Inspection) (2.4)

To verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

E. Product Quality Review (2.5)

Regular quality-reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or nonconformances and related investigations
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program

- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

III. PERSONNEL (3)

A. Personnel Qualifications (3.1)

There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.

The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

B. Personnel Hygiene (3.2)

Personnel should practice good sanitation and health habits.

Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed, when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and APIs from contamination.

Personnel should avoid direct contact with intermediates or APIs.

Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

C. Consultants (3.3)

Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

IV. BUILDINGS AND FACILITIES (4)

A. Design and Construction (4.1)

Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants, as appropriate.

Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection
- Quarantine before release or rejection of intermediates and APIs
- Sampling of intermediates and APIs
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
- Storage of released materials
- Production operations
- Packaging and labeling operations
- Laboratory operations

Adequate and clean washing and toilet facilities should be provided for personnel. These facilities should be equipped with hot and cold water, as appropriate, soap or detergent, air

dryers, or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process, intermediate, or API.

B. Utilities (4.2)

All utilities that could affect product quality (e.g., steam, gas, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

C. Water (4.3)

Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

If drinking (potable) water is insufficient to ensure API quality and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms, and/or endotoxins should be established.

Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

D. Containment (4.4)

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another.

Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials, such as herbicides and pesticides, should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

E. Lighting (4.5)

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

F. Sewage and Refuse (4.6)

Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

G. Sanitation and Maintenance (4.7)

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

V. PROCESS EQUIPMENT (5)

A. Design and Construction (5.1)

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance.

Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Production equipment should only be used within its qualified operating range.

Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter the quality of APIs or intermediates beyond the official or other established specifications. Any deviations from this practice should be evaluated to ensure that there are no detrimental effects on the material's fitness for use. Wherever possible, food grade lubricants and oils should be used.

Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

B. Equipment Maintenance and Cleaning (5.2)

Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

Written procedures should be established for cleaning equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment
- Cleaning schedules, including, where appropriate, sanitizing schedules
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning
- Instructions for the removal or obliteration of previous batch identification
- Instructions for the protection of clean equipment from contamination prior to use
- Inspection of equipment for cleanliness immediately before use, if practical
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate

Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms).

Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Equipment should be identified as to its contents and its cleanliness status by appropriate means.

C. Calibration (5.3)

Control, weighing, measuring, monitoring, and testing equipment critical for ensuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

Equipment calibrations should be performed using standards traceable to certified standards, if they exist.

Records of these calibrations should be maintained.

The current calibration status of critical equipment should be known and verifiable.

Instruments that do not meet calibration criteria should not be used.

Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an effect on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

D. Computerized Systems (5.4)

GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.

Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

Written procedures should be available for the operation and maintenance of computerized systems.

Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

Changes to computerized systems should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software, and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

Data can be recorded by a second means in addition to the computer system.

VI. DOCUMENTATION AND RECORDS (6)

A. Documentation System and Specifications (6.1)

All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.

The issuance, revision, superseding, and withdrawal of all documents should be controlled by maintaining revision histories.

A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still legible.

During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically affect quality. Acceptance criteria should be established and documented for in-process controls.

If electronic signatures are used on documents, they should be authenticated and secure.

B. Equipment Cleaning and Use Record (6.2)

Records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

If equipment is dedicated to manufacturing one intermediate or API, individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

C. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials (6.3)

Records should be maintained including:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
- The results of any test or examination performed and the conclusions derived from this
- Records tracing the use of materials
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

Master (approved) labels should be maintained for comparison to issued labels.

D. Master Production Instructions (Master Production and Control Records) (6.4)

To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for

each batch size or rate of production should be included. Variations to quantities should be included where they are justified

- The production location and major production equipment to be used
- Detailed production instructions, including the:

  - sequences to be followed

  - ranges of process parameters to be used

  - sampling instructions and in-process controls with their acceptance criteria, where appropriate

  - time limits for completion of individual processing steps and/or the total process, where appropriate

  - expected yield ranges at appropriate phases of processing or time
- Where appropriate, special notations and precautions to be followed, or cross-references to these
- The instructions for storage of the intermediate or API to ensure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

E. Batch Production Records (Batch Production and Control Records) (6.5)

Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to ensure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed

- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for intermediate or API
- Representative label of API or intermediate if made commercially available
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing

Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

F. Laboratory Control Records (6.6)

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing
- A statement of or reference to each test method used
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions
- A complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors
- A statement of the test results and how they compare with established acceptance criteria
- The signature of the person who performed each test and the date(s) the tests were performed
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards

Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices

- All stability testing performed on APIs
- Out-of-specification (OOS) investigations

G. Batch Production Record Review (6.7)

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

VII. MATERIALS MANAGEMENT (7)

A. General Controls (7.1)

There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

Materials should be purchased against an agreed specification, from a supplier, or suppliers, approved by the quality unit(s).

If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

B. Receipt and Quarantine (7.2)

Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the

supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use.

Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier

Large storage containers and their attendant manifolds, filling, and discharge lines should be appropriately identified.

Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

C. Sampling and Testing of Incoming Production Materials (7.3)

At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below. A *supplier's certificate of analysis* can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a complete analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.

Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company’s control do not need to be tested if the manufacturer’s certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based on a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

D. Storage (7.4)

Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

E. Re-evaluation (7.5)

Materials should be re-evaluated, as appropriate, to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

VIII. PRODUCTION AND IN-PROCESS CONTROLS (8)

A. Production Operations (8.1)

Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code
- Receiving or control number
- Weight or measure of material in the new container
- Re-evaluation or retest date if appropriate

Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

Other critical activities should be witnessed or subjected to an equivalent control.

Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Any deviation should be documented and explained. Any critical deviation should be investigated.

The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

B. Time Limits (8.2)

If time limits are specified in the master production instruction (see 6.40), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

C. In-process Sampling and Controls (8.3)

Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the developmental stage or from historical data.

The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

Critical in-process controls (and critical process monitoring), including control points and methods, should be stated in writing and approved by the quality unit(s).

In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

D. Blending Batches of Intermediates or APIs (8.4)

For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

Acceptable blending operations include, but are not limited to:

- Blending of small batches to increase batch size
- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch

Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications, where appropriate.

The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

E. Contamination Control (8.5)

Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials.

Precautions to avoid contamination should be taken when APIs are handled after purification.

IX. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES (9)

A. General (9.1)

There should be written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing, release, and handling of packaging and labeling materials.

Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

B. Packaging Materials (9.2)

Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

If containers are reused, they should be cleaned in accordance with documented procedures, and all previous labels should be removed or defaced.

C. Label Issuance and Control (9.3)

Access to the label storage areas should be limited to authorized personnel.

Procedures should be established to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

Obsolete and out-dated labels should be destroyed.

Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

A printed label representative of those used should be included in the batch production record.

D. Packaging and Labeling Operations (9.4)

There should be documented procedures designed to ensure that correct packaging materials and labels are used.

Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

Labels used on containers of intermediates or APIs should indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of intermediate or API.

If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, special transport conditions, and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

X. STORAGE AND DISTRIBUTION (10)

A. Warehousing Procedures (10.1)

Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.

B. Distribution Procedures (10.2)

APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Special transport or storage conditions for an API or intermediate should be stated on the label.

The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

XI. LABORATORY CONTROLS (11)

A. General Controls (11.1)

The independent quality unit(s) should have at its disposal adequate laboratory facilities.

There should be documented procedures describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include control of impurities (e.g., organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should include analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

Reagents and standard solutions should be prepared and labeled following written procedures. *Use by* dates should be applied, as appropriate, for analytical reagents or standard solutions.

Primary reference standards should be obtained, as appropriate, for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Where a primary reference standard is not available from an officially recognized source, an *in-house primary standard* should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

B. Testing of Intermediates and APIs (11.2)

For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed, and classification of each identified impurity (e.g., inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH guidance Q6B.

The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data to detect changes to the API

resulting from modifications in raw materials, equipment operating parameters, or the production process.

Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

C. Validation of Analytical Procedures - See Section 12. (11.3)

D. Certificates of Analysis (11.4)

Authentic certificates of analysis should be issued for each batch of intermediate or API on request.

Information on the name of the intermediate or API including, where appropriate, its grade, the batch number, and the date of release should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should show the name, address, and telephone number of the repacker/reprocessor and reference the name of the original manufacturer.

If new certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

E. Stability Monitoring of APIs (11.5)

A documented, on-going testing program should be established to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

The test procedures used in stability testing should be validated and be stability indicating.

Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of

the same material and in small-scale drums of similar or identical material composition to the market drums.

Normally, the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.

Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first 3 months, and at 3-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., 9-month testing) can be considered.

Where appropriate, the stability storage conditions should be consistent with the ICH guidances on stability.

F. Expiry and Retest Dating (11.6)

When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g., published data, test results).

An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) the quality of the API represents the material to be made on a commercial scale.

A representative sample should be taken for the purpose of performing a retest.

G. Reserve/Retention Samples (11.7)

The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the

batch, whichever is longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.

The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

XII. VALIDATION (12)

A. Validation Policy (12.1)

The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.

The critical parameters/attributes should normally be identified during the development stage or from historical data, and the necessary ranges for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes
- Identifying process parameters that could affect the critical quality attributes of the API
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control

Validation should extend to those operations determined to be critical to the quality and purity of the API.

B. Validation Documentation (12.2)

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g., retrospective, prospective, concurrent) and the number of process runs.

A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

Any variations from the validation protocol should be documented with appropriate justification.

C. Qualification (12.3)

Before initiating process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose

- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements

- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges

- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications

D. Approaches to Process Validation (12.4)

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

There are three approaches to validation. Prospective validation is the preferred approach, but there are situations where the other approaches can be used. These approaches and their applicability are discussed here.

Prospective validation should normally be performed for all API processes as defined in 12.1. Prospective validation of an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

An exception can be made for retrospective validation of well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

1. Critical quality attributes and critical process parameters have been identified

2. Appropriate in-process acceptance criteria and controls have been established

3. There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability

4. Impurity profiles have been established for the existing API

Batches selected for retrospective validation should be representative of all batches produced during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

E. Process Validation Program (12.5)

The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to, or better than, historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

F. Periodic Review of Validated Systems (12.6)

Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

G. Cleaning Validation (12.7)

Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable, and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

Equipment cleaning/sanitation studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

H. Validation of Analytical Methods (12.8)

Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

Methods should be validated to include consideration of characteristics included within the ICH guidances on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

Appropriate qualification of analytical equipment should be considered before initiating validation of analytical methods.

Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

XIII. CHANGE CONTROL (13)

A formal change control system should be established to evaluate all changes that could affect the production and control of the intermediate or API.

Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

Current dosage form manufacturers should be notified of changes from established production and process control procedures that can affect the quality of the API.

XIV. REJECTION AND RE-USE OF MATERIALS (14)

A. Rejection (14.1)

Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

B. Reprocessing (14.2)

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and over-reacted materials.

C. Reworking (14.3)

Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.

Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, a report can be written and the batch released once it is found to be acceptable.

Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

D. Recovery of Materials and Solvents (14.4)

Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or commingling with other approved materials.

Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

E. Returns (14.5)

Returned intermediates or APIs should be identified as such and quarantined.

If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

XV. COMPLAINTS AND RECALLS (15)

All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

Complaint records should include:

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of person submitting the complaint
- Complaint nature (including name and batch number of the API)
- Date complaint is received
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken
- Response provided to the originator of complaint (including date response sent)
- Final decision on intermediate or API batch or lot

Records of complaints should be retained to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

XVI. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) (16)

All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites.

There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party.

A contract should permit a company to audit its contractor's facilities for compliance with GMP.

Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

XVII. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS (17)

A. Applicability (17.1)

This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.

All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this guidance.

B. Traceability of Distributed APIs and Intermediates (17.2)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

C. Quality Management (17.3)

Agents, brokers, traders, distributors, repackers, or relabelers should establish, document and implement an effective system of managing quality, as specified in Section 2.

D. Repackaging, Relabeling, and Holding of APIs and Intermediates (17.4)

Repackaging, relabeling, and holding APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this guidance, to avoid mix-ups and loss of API or intermediate identity or purity.

Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

E. Stability (17.5)

Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

F. Transfer of Information (17.6)

Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

The agent, broker, trader, distributor, repacker, or relabeler who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context *authorized* refers to authorized by the manufacturer.)

The specific guidance for certificate of analysis included in Section 11.4 should be met.

G. Handling of Complaints and Recalls (17.7)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.

If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabelers should review the complaint with the original API or intermediate manufacturer to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original API or intermediate manufacturer (including date and information provided).

H. Handling of Returns (17.8)

Returns should be handled as specified in Section 14.5. The agents, brokers, traders, distributors, repackers, or relabelers should maintain documentation of returned APIs and intermediates.

XVIII. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION (18)

A. General (18.1)

Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for *classical* processes for production of small molecules and for processes using recombinant and nonrecombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

The term *biotechnological process* (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

The term *classical fermentation* refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by *classical fermentation* are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

Appropriate controls should be established at all stages of manufacturing to ensure intermediate and/or API quality. While this guidance starts at the cell culture/fermentation step, prior steps

(e.g., cell banking) should be performed under appropriate process controls. This guidance covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for determining environmental quality and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

In general, process controls should take into account:

- Maintenance of the working cell bank (where appropriate)
- Proper inoculation and expansion of the culture
- Control of the critical operating parameters during fermentation/cell culture
- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity, where appropriate
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production
- Viral safety concerns as described in ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*

Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

B. Cell Bank Maintenance and Record Keeping (18.2)

Access to cell banks should be limited to authorized personnel.

Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

Records of the use of the vials from the cell banks and storage conditions should be maintained.

Where appropriate, cell banks should be periodically monitored to determine suitability for use.

See ICH guidance Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

C. Cell Culture/Fermentation (18.3)

Where cell substrates, media, buffers, and gases are to be added under aseptic conditions, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

Personnel should be appropriately gowned and take special precautions handling the cultures.

Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, sanitized, or sterilized.

Culture media should be sterilized before use, when necessary, to protect the quality of the API.

Appropriate procedures should be in place to detect contamination and determine the course of action to be taken. Procedures should be available to determine the impact of the contamination on the product and to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified, as appropriate, and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

Records of contamination events should be maintained.

Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

D. Harvesting, Isolation and Purification (18.4)

Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption should be performed in equipment and areas designed to minimize the risk of contamination.

Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

E. Viral Removal/Inactivation steps (18.5)

See ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

Appropriate precautions should be taken to prevent potential viral contamination from previral to postviral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g., through equipment or environment) from previous steps.

XIX. APIs FOR USE IN CLINICAL TRIALS (19)

A. General (19.1)

Not all the controls in the previous sections of this guidance are appropriate for the manufacture of a new API for investigational use during its development. Section XIX (19) provides specific guidance unique to these circumstances.

The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

B. Quality (19.2)

Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for approval of each batch.

A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

Process and quality problems should be evaluated.

Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

C. Equipment and Facilities (19.3)

During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.

Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

D. Control of Raw Materials (19.4)

Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier’s analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

E. Production (19.5)

The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

F. Validation (19.6)

Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification ensures API quality during this development phase.

Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

G. Changes (19.7)

Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

H. Laboratory Controls (19.8)

While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

I. Documentation (19.9)

A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY (20)

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) ***(or Drug Substance):*** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Batch (or Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden: The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with results produced by a reference or traceable standard over an appropriate range of measurements.

Computer System: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System: A process or operation integrated with a computer system.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging, or repackaging, storage or transport.

Contract Manufacturer: A manufacturer who performs some aspect of manufacturing on behalf of the original manufacturer.

Critical: Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination: Contamination of a material or product with another material or product.

Deviation: Departure from an approved instruction or established standard.

Drug (Medicinal) Product: The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance: See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date): The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions and after which it should not be used.

Impurity: Any component present in the intermediate or API that is not the desired entity.

Impurity Profile: A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control): Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this guidance only addresses those intermediates produced after the point that a company has defined as the point at which the production of the API begins.)

Lot: See Batch

Lot Number: See *Batch Number*

Manufacture: All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Material: A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It can be used for further processing.

Packaging Material: Any material intended to protect an intermediate or API during storage and transport.

Procedure: A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids: Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon).

Process Control: See ***In-Process Control.***

Production: All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA): The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC): Checking or testing that specifications are met.

Quality Unit(s): An organizational unit independent of production that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material: A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary: A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary: A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete, is considered to be part of the normal process, and is not reprocessing.

Retest Date: The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed): See definition for signed.

Signed (signature): The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent: An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. *Conformance to specification* means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Validation Protocol: A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and/or operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical: The quantity that would be produced at any appropriate phase of production based upon the quantity of material to be used, in the absence of any loss or error in actual production.

Exhibit C

Examples of FDA-Approved Drugs That Contain Racemates[1]

Generic Name	Brand Name	Active Ingredient	Approval Date
acebutolol hydrochloride	Sectral	± acebutolol hydrochloride	Dec. 28, 1984
albuterol sulfate[2]	**Proventil HFA**	**± albuterol sulfate**	**Aug. 15, 1996**
almotriptan malate	Axert	± almotriptan malate	May 7, 2001
amlodipine besylate	Norvasc	± amlodipine besylate	July 31, 1992
amphetamine aspartate monohydrate	Adderall	±amphetamine aspartate monohydrate	Feb. 13, 1996
atenolol	Tenormin	± atenolol	Prior to Jan. 1, 1982
atropine sulfate	Lomotil	± atropine sulfate	Prior to Jan. 1, 1982
azelastine hydrochloride	Astelin	± azelastine hydrochloride	Nov. 1, 1996
baclofen	Lioresal	± baclofen	June 17, 1992
betaxolol hydrochloride[3]	Kerlone	± betaxolol hydrochloride	Oct. 27, 1989
bupivacaine hydrochloride	Sensorcaine/ Marcaine HCL	± bupivacaine hydrochloride	Prior to Jan. 1, 1982
bupropion hydrochloride	Wellbutrin	± bupropion hydrochloride	Prior to Jan. 1, 1982
candesartan cilexetil	Atacand	± candesartan cilexetil	June 4, 1998
carisoprodol	SOMA	± carisoprodol	Prior to Jan. 1, 1982
carvedilol	Coreg	± carvedilol	Sept. 14, 1995
cetirizine hydrochloride	Zyrtec-D	± cetirizine hydrochloride	Aug. 10, 2001
citalopram hydrobromide[4]	Celexa	± citalopram hydrobromide	Apr. 27, 2000
disopyramide phosphate	Norpace	± disopyramide phosphate	Prior to Jan. 1, 1982
dobutamine hydrochloride	Dobutrex	± dobutamine hydrochloride	Prior to Jan. 1, 1982
donepezil hydrochloride	Aricept	± donepezil hydrochloride	Nov. 25, 1996

[1] Attached to this chart as Exhibit C1-C7 are examples of the Orange Book listings and approved labeling for selected racemates in the chart. These racemates are indicated in **bold** in the chart.

[2] One of the enantiomers of the racemate albuterol is levalbuterol (which was approved to be marketed as Xopenex).

[3] One of the enantiomers of the racemate betaxolol is levobetaxolol (which was approved to be marketed as Betaxon).

[4] One of the enantiomers of the racemate citalopram is escitalopram (which was approved to be marketed as Lexapro).

esmolol hydrochloride	Brevibloc	± esmolol hydrochloride	Feb. 16, 2001
ethopropazine hydrochloride	Parsidol	± ethopropazine hydrochloride	Prior to Jan. 1, 1982
etodolac	Lodine	± etodolac	Jan. 31, 1991
fenfluramine hydrochloride[5]	Pondimin	± fenfluramine hydrochloride	1973
fenoldopam mesylate	Corlopam	± fenoldopam mesylate	Sept. 23, 1997
fenoprofen calcium	Nalfon	± fenoprofen calcium	Prior to Jan. 1, 1982
fexofenadine hydrochloride	Allegra	± fexofenadine hydrochloride	July 25, 1996
fluoxetine hydrochloride	**Prozac**	**± fluoxetine hydrochloride**	**Dec. 29, 1987**
flurbiprofen	Ansaid	± flurbiprofen	Oct. 31, 1988
fluvastatin sodium	Lescol	± fluvastatin sodium	Dec. 31, 1993
formoterol fumerate	Foradil	± formoterol fumerate	Feb. 16, 2001
gatifloxacin	Zymar	± gatifloxacin	Mar. 28, 2003
ibuprofen	Motrin	± ibuprofen	Prior to Jan. 1, 1982
ibuprofen lysine	Neoprofen	± ibuprofen lysine	Apr. 13, 2006
ipratropium bromide	Atroven	± ipratropium bromide	Sept. 29, 1993
itraconazole	Sporanox	± itraconazole	Sept. 11, 1992
labetalol hydrochloride	Normodyne	± labetalol hydrochloride	Aug. 1, 1984
lenalidomide	Revlimid	± lenalidomide	Dec. 27, 2005
malathion	Ovide	± malathion	Aug. 2, 1982
mefloquine hydrochloride	Lariam	± mefloquine hydrochloride	May 2, 1989
metaproterenol sulfate	Alupent	± metaproterenol sulfate	Prior to Jan. 1, 1982
methohexital sodium	Brevital Sodium	± methohexital sodium	Prior to Jan. 1, 1982
methylphenidate hydrochloride	Ritalin	± methylphenidate hydrochloride	Prior to Jan. 1, 1982
metoprolol tartrate	Lopressor	± metoprolol tartrate	Prior to Jan. 1, 1982
midodrine hydrochloride	Proamatine	± midodrine hydrochloride	Sept. 6, 1996
mirtazapine	Remeron	± mirtazapine	June 14, 1996
misoprostol	**Cytotec**	**± misoprostol**	**Dec. 27, 1988**
modafinil	Provigil	± modafinil	Dec. 24, 1998
nabilone	Cesamet	± nabilone	Dec. 26, 1985
nebivolol hydrochloride	**Bystolic**	**± nebivolol hydrochloride**	**Dec. 17, 2007**
nicardipine hydrochloride	Cardene	± nicardipine hydrochloride	Jan. 30, 1992

[5] One of the enantiomers of the racemate fenfluramine is dexfenfluramine (which was approved to be marketed as Redux).

norgestrel	Lo/Ovral	±norgestrel	Prior to Jan. 1, 1982
ofloxacin	Floxin	± ofloxacin	Dec. 28, 1990
omeprazole[6]	**Prilosec**	**± omeprazole**	**Sept. 14, 1989**
ondansetron hydrochloride	Zofran	± ondansetron hydrochloride	Jan. 4, 1991
oxybutynin	Oxytrol	± oxybutynin	Feb. 26, 2003
oxybutynin chloride	**Ditropan**	**± oxybutynin chloride**	**Prior to Jan. 1, 1982**
phenprocoumon	Liquamar	± phenprocoumon	Prior to Jan. 1, 1982
pioglitazone hydrochloride	Actos	± pioglitazone hydrochloride	July 15, 1999
promethazine hydrochloride	Phenergan	± pioglitazone hydrochloride	Prior to Jan. 1, 1982
propafenone hydrochloride	Rythmol SR	± propafenone hydrochloride	Sept. 4, 2003
propranolol hydrochloride	Inderal	± propranolol hydrochloride	Prior to Jan. 1, 1982
ranolazine	Randexa	± ranolazine	Feb. 12, 2007
rosiglitazone maleate	Avandia	± rosiglitazone maleate	May 25, 1999
sibutramine hydrochloride	Meridia	± sibutramine hydrochloride	Nov. 22, 1997
sotalol	Betapace	± sotalol	Oct. 30, 1992
thalidomide	Thalomid	± thalidomide	July 16, 1998
thioridazine hydrochloride	Mellaril	± thioridazine hydrochloride	Prior to Jan. 1, 1982
tramadol hydrochloride	**Ultram**	**± thioridazine hydrochloride**	**Mar. 3, 1995**
tranylcypromine sulfate	Parnate	± tranylcypromine sulfate	Aug. 16, 1985
trimeprazine tartrate	Temaril	± trimeprazine tartrate	Prior to Jan. 1, 1982
trimipramine maleate	Surmontil	± trimipramine maleate	Prior to Jan. 1, 1982
venlafaxine hydrochloride	Effexor	± venlafaxine hydrochloride	Dec. 28, 1993
verapamil hydrochloride	Verelan	± verapamil hydrochloride	Nov. 25, 1998
warfarin sodium	Coumadin	± warfarin sodium	Prior to Jan. 1, 1982
zileuton	Zyflo	± zileuton	Dec. 9, 1996

[6] One of the enantiomers of the racemate omeprazole is esomeprazole (which was approved to be marketed as Nexium).

Exhibit C1

Search results from the "OB_Rx" table for query on "020503."

Active Ingredient:	ALBUTEROL SULFATE
Dosage Form;Route:	AEROSOL, METERED; INHALATION
Proprietary Name:	PROVENTIL-HFA
Applicant:	3M
Strength:	EQ 0.09MG BASE/INH
Application Number:	020503
Product Number:	001
Approval Date:	Aug 15, 1996
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	View

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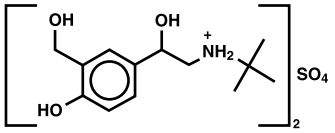
Orange Book Data Updated Through September, 2008
Patent and Generic Drug Product Data Last Updated: October 24, 2008

PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol

FOR ORAL INHALATION ONLY

Prescribing Information

DESCRIPTION The active component of PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol is albuterol sulfate, USP racemic α[1][(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α´-diol sulfate (2:1)(salt), a relatively selective beta$_2$-adrenergic bronchodilator having the following chemical structure:



Albuterol sulfate is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol sulfate. The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. Albuterol sulfate is a white to off-white crystalline solid. It is soluble in water and slightly soluble in ethanol. PROVENTIL HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane), ethanol, and oleic acid.

Each actuation delivers 120 mcg albuterol sulfate, USP from the valve and 108 mcg albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each canister provides 200 inhalations. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see **WARNINGS**, **Cardiovascular Effects** section).

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380-1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (Tmax) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

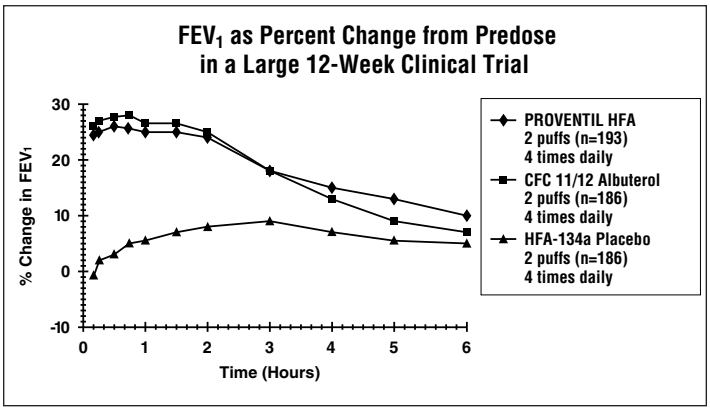
Pharmacokinetics In a single-dose bioavailability study which enrolled six healthy, male volunteers, transient low albuterol levels (close to the lower limit of quantitation) were observed after administration of two puffs from both PROVENTIL® HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler. No formal pharmacokinetic analyses were possible for either treatment, but systemic albuterol levels appeared similar.

Clinical Trials In a 12-week, randomized, double-blind, double-dummy, active- and placebo-controlled trial, 565 patients with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA Inhalation Aerosol (193 patients) in comparison to a CFC 11/12 propelled albuterol inhaler (186 patients) and an HFA-134a placebo inhaler (186 patients).

Serial FEV_1 measurements (shown below as percent change from test-day baseline) demonstrated that two inhalations of PROVENTIL HFA Inhalation Aerosol produced significantly greater improvement in pulmonary function than placebo and produced outcomes which were clinically comparable to a CFC 11/12 propelled albuterol inhaler.

The mean time to onset of a 15% increase in FEV_1 was 6 minutes and the mean time to peak effect was 50 to 55 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 was 3 hours. In some patients, duration of effect was as long as 6 hours.

In another clinical study in adults, two inhalations of PROVENTIL HFA Inhalation Aerosol taken 30 minutes before exercise prevented exercise-induced bronchospasm as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients.



In a 4-week, randomized, open-label trial, 63 children, 4 to 11 years of age, with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA Inhalation Aerosol (33 pediatric patients) in comparison to a CFC 11/12 propelled albuterol inhaler (30 pediatric patients).

Serial FEV_1 measurements as percent change from test-day baseline demonstrated that two inhalations of PROVENTIL HFA Inhalation Aerosol produced outcomes which were clinically comparable to a CFC 11/12 propelled albuterol inhaler.

The mean time to onset of a 12% increase in FEV_1 for PROVENTIL HFA Inhalation Aerosol was 7 minutes and the mean time to peak effect was approximately 50 minutes. The mean duration of effect as measured by a 12% increase in FEV_1 was 2.3 hours. In some pediatric patients, duration of effect was as long as 6 hours.

In another clinical study in pediatric patients, two inhalations of PROVENTIL HFA Inhalation Aerosol taken 30 minutes before exercise provided comparable protection against exercise-induced bronchospasm as a CFC 11/12 propelled albuterol inhaler.

INDICATIONS AND USAGE PROVENTIL® HFA Inhalation Aerosol is indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

CONTRAINDICATIONS PROVENTIL® HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol or any other PROVENTIL HFA components.

WARNINGS

1. Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL® HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

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2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROVENTIL HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

3. Use of Anti-inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, eg, corticosteroids, to the therapeutic regimen.

4. Cardiovascular Effects: PROVENTIL HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROVENTIL HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROVENTIL HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

PRECAUTIONS

General Albuterol sulfate, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients See illustrated **Patient's Instructions for Use**. SHAKE WELL BEFORE USING. Patients should be given the following information:

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILDUP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

The mouthpiece should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. The mouthpiece must be shaken to remove excess water, then air dried thoroughly (such as overnight). Blockage from medication buildup or improper medication delivery may result from failure to thoroughly air dry the mouthpiece.

If the mouthpiece should become blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing as described above.

If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, test spray twice away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly.

The action of PROVENTIL® HFA Inhalation Aerosol should last up to 4 to 6 hours. PROVENTIL HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of PROVENTIL HFA Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician.

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about use of PROVENTIL HFA Inhalation Aerosol. Effective and safe use of PROVENTIL HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use PROVENTIL HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been used.

In general, the technique for administering PROVENTIL HFA Inhalation Aerosol to children is similar to that for adults. Children should use PROVENTIL HFA Inhalation Aerosol under adult supervision, as instructed by the patient's physician (see **Patient's Instructions for Use**).

Drug Interactions

1. Beta-Blockers: Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROVENTIL HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, eg, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia which may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

3. Albuterol-Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear; nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: PROVENTIL HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility In a 2-year study in SPRAGUE DAWLEY® rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1700 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 800 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22-month study in Golden Hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 110 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy *Teratogenic Effects* Pregnancy Category C Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg dose (approximately 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in SPRAGUE DAWLEY rats, the albuterol sulfate/HFA-134a formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 70 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

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A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of PROVENTIL HFA Inhalation Aerosol or albuterol sulfate in pregnant women. PROVENTIL HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Nursing Mothers Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROVENTIL HFA Inhalation Aerosol are excreted in human milk.

Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROVENTIL HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when albuterol sulfate is administered to a nursing woman.

Pediatrics The safety and effectiveness of PROVENTIL HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

Geriatrics PROVENTIL HFA Inhalation Aerosol has not been studied in a geriatric population. As with other $beta_2$-agonists, special caution should be observed when using PROVENTIL HFA Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

ADVERSE REACTIONS Adverse reaction information concerning PROVENTIL® HFA Inhalation Aerosol is derived from a 12-week, double-blind, double-dummy study which compared PROVENTIL HFA Inhalation Aerosol, a CFC 11/12 propelled albuterol inhaler, and an HFA-134a placebo inhaler in 565 asthmatic patients. The following table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROVENTIL HFA Inhalation Aerosol treatment group and more frequently in the PROVENTIL HFA Inhalation Aerosol treatment group than in the placebo group. Overall, the incidence and nature of the adverse reactions reported for PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler were comparable.

Adverse Experience Incidences (% of patients) in a Large 12-week Clinical Trial*

Body System/Adverse Event (Preferred Term)		PROVENTIL® HFA Inhalation Aerosol (N = 193)	CFC 11/12 Propelled Albuterol Inhaler (N = 186)	HFA-134a Placebo Inhaler (N = 186)
Application Site Disorders	Inhalation Site Sensation	6	9	2
	Inhalation Taste Sensation	4	3	3
Body as a Whole	Allergic Reaction/Symptoms	6	4	<1
	Back Pain	4	2	3
	Fever	6	2	5
Central and Peripheral Nervous System	Tremor	7	8	2
Gastrointestinal System	Nausea	10	9	5
	Vomiting	7	2	3
Heart Rate and Rhythm Disorder	Tachycardia	7	2	<1
Psychiatric Disorders	Nervousness	7	9	3
Respiratory System Disorders	Respiratory Disorder (unspecified)	6	4	5
	Rhinitis	16	22	14
	Upper Resp Tract Infection	21	20	18
Urinary System Disorder	Urinary Tract Infection	3	4	2

*This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROVENTIL HFA Inhalation Aerosol group and more frequently in the PROVENTIL HFA Inhalation Aerosol group than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 3% of the patients receiving PROVENTIL HFA Inhalation Aerosol, and by a greater proportion of PROVENTIL HFA Inhalation Aerosol patients than placebo patients, which have the potential to be related to PROVENTIL HFA Inhalation Aerosol include: dysphonia, increased sweating, dry mouth, chest pain, edema, rigors, ataxia, leg cramps, hyperkinesia, eructation, flatulence, tinnitus, diabetes mellitus, anxiety, depression, somnolence, rash. Palpitation and dizziness have also been observed with PROVENTIL HFA Inhalation Aerosol.

Adverse events reported in a 4-week pediatric clinical trial comparing PROVENTIL HFA Inhalation Aerosol and a CFC 11/12 propelled albuterol inhaler occurred at a low incidence rate and were similar to those seen in the adult trials.

In small, cumulative dose studies, tremor, nervousness, and headache appeared to be dose related.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, headache, and drying or irritation of the oropharynx.

OVERDOSAGE The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under **ADVERSE REACTIONS**, eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROVENTIL® HFA Inhalation Aerosol. Treatment consists of discontinuation of PROVENTIL HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 6800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is two inhalations repeated every 4 to 6 hours. More frequent administration

PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol

or a larger number of inhalations is not recommended. In some patients, one inhalation every 4 hours may be sufficient. Each actuation of PROVENTIL® HFA Inhalation Aerosol delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

Exercise Induced Bronchospasm Prevention The usual dosage for adults and children 4 years of age and older is two inhalations 15 to 30 minutes before exercise.

To maintain proper use of this product, it is important that the mouthpiece be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly (see **PRECAUTIONS**, **Information for Patients** section). Keeping the plastic mouthpiece clean is very important to prevent medication buildup and blockage. The inhaler may cease to deliver medication if not properly cleaned and air dried thoroughly. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage.

If a previously effective dose regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

HOW SUPPLIED PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol is supplied as a pressurized aluminum canister with a yellow plastic actuator and orange dust cap each in boxes of one. Each actuation delivers 120 mcg of albuterol sulfate from the valve and 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base). Canisters with a labeled net weight of 6.7 g contain 200 inhalations (NDC 0085-1132-01).

Rx only. Store between 15°-25°C (59°-77°F). For best results, canister should be at room temperature before use.

SHAKE WELL BEFORE USING.

The yellow actuator supplied with PROVENTIL HFA Inhalation Aerosol should not be used with any other product canisters, and actuator from other products should not be used with a PROVENTIL HFA Inhalation Aerosol canister. The correct amount of medication in each canister cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used.

WARNING Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.

PROVENTIL® HFA Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

Developed and Manufactured by
3M Health Care Limited
Loughborough UK
or
3M Drug Delivery Systems
Northridge, CA 91324
or
Laboratoires 3M
Santé Pithiviers FR
for

Schering Corporation,
Kenilworth, NJ 07033 USA

PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol

FOR ORAL INHALATION ONLY

Patient's Instructions for Use

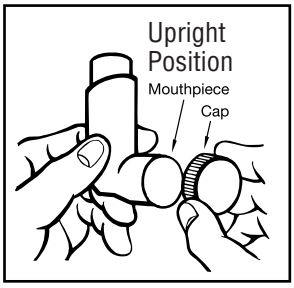


Figure 1

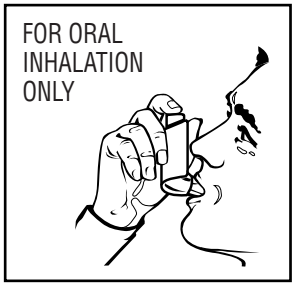


Figure 2

Before using your PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol, read complete instructions carefully. Children should use PROVENTIL HFA Inhalation Aerosol under adult supervision, as instructed by the patient's doctor.

Please note that CFC indicates that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece** (see Figure 1). **Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully inserted into the actuator.
2. As with all aerosol medications, it is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Prime by releasing four "test sprays" into the air, away from your face.
3. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (see Figure 2) and closing the lips around it.
4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2).
5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.
6. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again, and repeat steps 2 through 4. Replace the cap after use.
7. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILDUP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED.

   Routine cleaning instructions:

   Step 1. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with warm running water for 30 seconds at least once a week (see Figure A). **Never immerse the metal canister in water.**

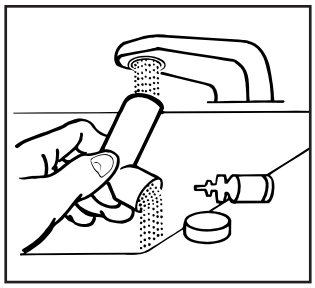


Figure A
Wash mouthpiece under warm running water.

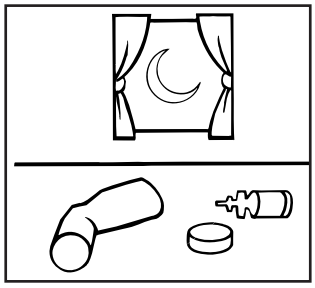


Figure B
Allow mouthpiece to air dry, such as overnight.

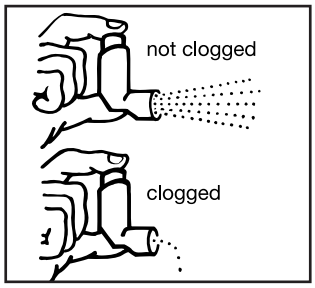


Figure C
When blocked, little or no medicine comes out.

   Step 2. To dry, shake off excess water and let the mouthpiece air dry thoroughly, such as overnight (see Figure B). When the mouthpiece is dry, replace the canister and the mouthpiece cap. Blockage from medication buildup is more likely to occur if the mouthpiece is not allowed to air dry thoroughly.

   IF YOUR INHALER HAS BECOME BLOCKED (little or no medication coming out of the mouthpiece, see Figure C), wash the mouthpiece as described in Step 1 and air dry thoroughly as described in Step 2.

   IF YOU NEED TO USE YOUR INHALER BEFORE IT IS COMPLETELY DRY, SHAKE OFF EXCESS WATER, replace the canister, and test spray twice into the air, away from your face, to remove most of the water remaining in the mouthpiece. Then take your dose as prescribed. **After such use, rewash and air dry thoroughly as described in Steps 1 and 2.**
8. The correct amount of medication in each inhalation cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used. Before you reach the specific number of actuations, you should consult your physician to determine whether a refill is

needed. Just as you should not take extra doses without consulting your physician, you also should not stop using PROVENTIL HFA Inhalation Aerosol without consulting your physician.

You may notice a slightly different taste or spray force than you are used to with PROVENTIL HFA Inhalation Aerosol, compared to other albuterol inhalation aerosol products.

DOSAGE:
Use only as directed by your physician.

WARNINGS:
The action of PROVENTIL® HFA Inhalation Aerosol should last up to 4 to 6 hours. PROVENTIL HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the number of puffs or frequency of doses of PROVENTIL HFA Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA Inhalation Aerosol, other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of PROVENTIL HFA Inhalation Aerosol.

Common adverse effects of treatment with PROVENTIL HFA Inhalation Aerosol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and safe use of PROVENTIL HFA Inhalation Aerosol includes an understanding of the way that it should be administered. Use PROVENTIL HFA Inhalation Aerosol only with the yellow actuator supplied with the product. The PROVENTIL HFA Inhalation Aerosol actuator should not be used with other aerosol medications.

For best results, use at room temperature. Avoid exposing product to extreme heat and cold.

Shake well before use.

Contents Under Pressure.
Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Store between 15°-25°C (59°-77°F). Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol does not contain chlorofluorocarbons (CFCs) as the propellant. Instead, the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

PROVENTIL® HFA (albuterol sulfate) Inhalation Aerosol

Developed and Manufactured by
3M Health Care Limited
Loughborough UK

or

3M Drug Delivery Systems
Northridge, CA 91324

or

Laboratoires 3M
Santé Pithiviers FR
for

Schering Corporation,
Kenilworth, NJ 07033 USA

Rev. 11/07 673700

U.S. Patent Nos. 5,225,183; 5,439,670; 5,605,674; 5,695,743; 5,766,573; and 6,352,684.

Exhibit C2

Search results from the "OB_Rx" table for query on "018936."

Active Ingredient:	FLUOXETINE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	PROZAC
Applicant:	LILLY
Strength:	EQ 20MG BASE
Application Number:	018936
Product Number:	001
Approval Date:	Dec 29, 1987
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB1**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	FLUOXETINE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	PROZAC
Applicant:	LILLY
Strength:	EQ 40MG BASE
Application Number:	018936
Product Number:	003
Approval Date:	Jun 15, 1999
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	FLUOXETINE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	PROZAC
Applicant:	LILLY
Strength:	EQ 10MG BASE
Application Number:	018936
Product Number:	006
Approval Date:	Dec 23, 1992
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB1**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	FLUOXETINE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	SARAFEM
Applicant:	LILLY
Strength:	EQ 10MG BASE

Application Number:	018936
Product Number:	007
Approval Date:	Jul 6, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB2**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	FLUOXETINE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	SARAFEM
Applicant:	LILLY
Strength:	EQ 20MG BASE
Application Number:	018936
Product Number:	008
Approval Date:	Jul 6, 2000
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB2**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through September, 2008

Patent and Generic Drug Product Data Last Updated: October 24, 2008

PV 5326 DPP

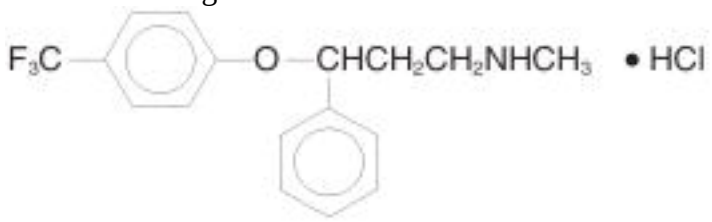
PROZAC®
FLUOXETINE CAPSULES, USP
FLUOXETINE ORAL SOLUTION, USP
FLUOXETINE DELAYED-RELEASE CAPSULES, USP

WARNING

Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Prozac or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (*See* WARNINGS, Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, *and* PRECAUTIONS, Pediatric Use.)

DESCRIPTION

Prozac® (fluoxetine capsules, USP and fluoxetine oral solution, USP) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem®, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

Prozac Weekly™ capsules, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant, antiobsessive compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion

Systemic bioavailability — In man, following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. Prozac Weekly capsules, a delayed-release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate-release formulations.

Protein binding — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* PRECAUTIONS).

Enantiomers — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism — Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical issues related to metabolism/elimination — The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as

"poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors (SSRIs), involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* Drug Interactions *under* PRECAUTIONS).

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac.

Weekly dosing — Administration of Prozac Weekly once weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20-mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20-mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen.

C_{max} for fluoxetine following the 90-mg dose was approximately 1.7-fold higher than the C_{max} value for the established 20-mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90-mg once-weekly dose and the last 20-mg

once-daily dose were separated by 1 week, C_{max} values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90-mg weekly dose and the last 20-mg once-daily dose by 1 week (*see* DOSAGE AND ADMINISTRATION).

Liver disease — As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Renal disease — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (*see* Use in Patients with Concomitant Illness *under* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Age

Geriatric pharmacokinetics — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Pediatric pharmacokinetics (children and adolescents) — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated

extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

CLINICAL TRIALS

Major Depressive Disorder

Daily Dosing

Adult — The efficacy of Prozac for the treatment of patients with major depressive disorder (≥18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing Prozac 20 mg and placebo have shown Prozac 20 mg daily to be effective in the treatment of elderly patients (≥60 years of age) with major depressive disorder. In these studies, Prozac produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤8. Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of major depressive disorder by DSM-III-R criteria) by the end of an initial 12-week open-treatment phase on Prozac 20 mg/day. These patients (N=298) were randomized to continuation on double-blind Prozac 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depressive disorder for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients taking Prozac compared with those on placebo.

Pediatric (children and adolescents) — The efficacy of Prozac 20 mg/day for the treatment of major depressive disorder in pediatric outpatients (N=315 randomized; 170 children ages 8 to <13, 145 adolescents ages 13 to ≤18) has been studied in two 8- to 9-week placebo-controlled clinical trials.

In both studies independently, Prozac produced a statistically significantly greater mean change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline to endpoint than did placebo.

Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness on the basis of age or gender.

Weekly dosing for maintenance/continuation treatment

A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded (defined as having a modified HAMD-17 score of ≤9, a CGI-Severity rating of ≤2, and no longer meeting criteria for major depressive disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with Prozac 20 mg once daily. These patients were randomized to double-blind, once-weekly continuation treatment with Prozac Weekly, Prozac 20 mg once daily, or placebo. Prozac Weekly once weekly and Prozac 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared with placebo for a period of 25 weeks. However, the equivalence of these 2 treatments during continuation therapy has not been established.

Obsessive Compulsive Disorder

Adult — The effectiveness of Prozac for the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once-a-day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. While there was no indication of a dose-response relationship for effectiveness in Study 1, a dose-response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined:

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies

		Prozac		
Outcome Classification	Placebo	20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No change	64%	41%	33%	29%
Minimally improved	17%	23%	28%	24%
Much improved	8%	28%	27%	28%
Very much improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Pediatric (children and adolescents) — In one 13-week clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD, patients received Prozac 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. Prozac produced a statistically significantly greater mean change from baseline to endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Bulimia Nervosa

The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, Prozac 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg versus placebo was present as early as Week 1

and persisted throughout each study. The Prozac-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between Prozac 60 mg and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

In a longer-term trial, 150 patients meeting DSM-IV criteria for bulimia nervosa, purging subtype, who had responded during a single-blind, 8-week acute treatment phase with Prozac 60 mg/day, were randomized to continuation of Prozac 60 mg/day or placebo, for up to 52 weeks of observation for relapse. Response during the single-blind phase was defined by having achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during the double-blind phase was defined as a persistent return to baseline vomiting frequency or physician judgment that the patient had relapsed. Patients receiving continued Prozac 60 mg/day experienced a significantly longer time to relapse over the subsequent 52 weeks compared with those receiving placebo.

Panic Disorder

The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.

Study 1 (N=180 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 42% versus 28%, respectively.

Study 2 (N=214 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% versus 44%, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder

Prozac is indicated for the treatment of major depressive disorder.

Adult — The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (*see* CLINICAL TRIALS).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.

The efficacy of Prozac 20 mg once daily in maintaining a response in major depressive disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial.

The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection from relapse as that provided by Prozac 20 mg daily (*see* CLINICAL TRIALS).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (*see* CLINICAL TRIALS).

The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended periods should be reevaluated periodically.

Obsessive Compulsive Disorder

Adult — Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of OCD (*see* CLINICAL TRIALS).

OCD is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in a 13-week, dose titration, clinical trial in patients with OCD, as defined in DSM-IV (*see* CLINICAL TRIALS).

Bulimia Nervosa

Prozac is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa.

The efficacy of Prozac was established in 8- to 16-week trials for adult outpatients with moderate to severe bulimia nervosa, i.e., at least 3 bulimic episodes per week for 6 months (*see* CLINICAL TRIALS).

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (*see* CLINICAL TRIALS). Nevertheless, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Panic Disorder

Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (*see* CLINICAL TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 or more of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) fear of losing control; 10) fear of dying; 11) paresthesias (numbness or tingling sensations); 12) chills or hot flashes.

The effectiveness of Prozac in long-term use, i.e., for more than 12 weeks, has not been established in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Prozac is contraindicated in patients known to be hypersensitive to it.

Monoamine oxidase inhibitors — There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY)] should be allowed after stopping Prozac before starting an MAOI.

Pimozide — Concomitant use in patients taking pimozide is contraindicated (*see* PRECAUTIONS).

Thioridazine — Thioridazine should not be administered with Prozac or within a minimum of 5 weeks after Prozac has been discontinued (*see* WARNINGS).

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others)

showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are

experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with Prozac, for a description of the risks of discontinuation of Prozac).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Prozac should be written for the smallest quantity of capsules, or liquid consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that Prozac is approved in the pediatric population only for major depressive disorder and obsessive compulsive disorder.

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Prozac is not approved for use in treating bipolar depression.

Rash and Possibly Allergic Events — In US fluoxetine clinical trials as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Serotonin Syndrome — The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Prozac treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Prozac with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS *and* Drug Interactions *under* PRECAUTIONS).

If concomitant treatment Prozac with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* Drug Interactions *under* PRECAUTIONS).

The concomitant use of Prozac with serotonin precursors (such as tryptophan) is not recommended (*see* Drug Interactions *under* PRECAUTIONS).

Potential Interaction with Thioridazine — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS).

PRECAUTIONS

General

Abnormal Bleeding — SSRIs and SNRIs, including fluoxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation (*see* Drug Interactions).

Anxiety and Insomnia — In US placebo-controlled clinical trials for major depressive disorder, 12% to 16% of patients treated with Prozac and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported, respectively, in 15% and 11% of patients treated with Prozac 60 mg and in 9% and 5% of patients treated with placebo.

Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (*see* Table 4).

Altered Appetite and Weight — Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with Prozac.

In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with Prozac because of anorexia (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with Prozac 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

Activation of Mania/Hypomania — In US placebo-controlled clinical trials for major depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of major depressive disorder (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with Prozac and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania (*see also* Pediatric Use *under* PRECAUTIONS).

Hyponatremia — Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Prozac. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Prozac was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also,

patients taking diuretics or who are otherwise volume depleted may be at greater risk (*see* Geriatric Use). Discontinuation of Prozac should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Seizures — In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Prozac should be introduced with care in patients with a history of seizures.

The Long Elimination Half-Lives of Fluoxetine and its Metabolites — Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Use in Patients with Concomitant Illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (*see* Renal disease *under* CLINICAL PHARMACOLOGY). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (*see* DOSAGE AND ADMINISTRATION).

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference with Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Discontinuation of Treatment with Prozac — During marketing of Prozac and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous

reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Prozac. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug (*see* DOSAGE AND ADMINISTRATION).

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Prozac and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available for Prozac. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Prozac.

Clinical Worsening and Suicide Risk — Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Serotonin Syndrome — Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Prozac and triptans, tramadol or other serotonergic agents.

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

Abnormal Bleeding— Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding (*see* PRECAUTIONS, Abnormal Bleeding).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs metabolized by CYP2D6 — Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS *and* WARNINGS).

Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

CNS active drugs — The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug

interaction or QT_c prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT_c prolongation warrants restricting the concurrent use of pimozide and Prozac. Concomitant use of Prozac and pimozide is contraindicated (*see* CONTRAINDICATIONS). For thioridazine, see CONTRAINDICATIONS and WARNINGS.

Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

Other drugs effective in the treatment of major depressive disorder — In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY, *and* Drugs metabolized by CYP2D6 *under* Drug Interactions).

Serotonergic drugs — Based on the mechanism of action of SNRIs and SSRIs, including Prozac, and the potential for serotonin syndrome, caution is advised when Prozac is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* Serotonin Syndrome *under* WARNINGS). The concomitant use of Prozac with other SSRIs, SNRIs or tryptophan is not recommended (*see* Tryptophan).

Triptans — There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Prozac with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* Serotonin Syndrome *under* WARNINGS).

Potential effects of coadministration of drugs tightly bound to plasma proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly-bound drugs (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs that interfere with hemostasis (e.g., NSAIDs, Aspirin, Warfarin) — Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs

are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued.

Electroconvulsive therapy (ECT) — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed.

Carcinogenicity — The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis], produced no evidence of carcinogenicity.

Mutagenicity — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of fertility — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility (*see* Pediatric Use).

Pregnancy

Pregnancy Category C — In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m^2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis). Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects — Neonates exposed to Prozac and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* Monoamine oxidase inhibitors *under* CONTRAINDICATIONS).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836

women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Prozac during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (*see* DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery

The effect of Prozac on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Pediatric Use

The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18 (*see* CLINICAL TRIALS).

The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 (*see* CLINICAL TRIALS).

The safety and effectiveness in pediatric patients <8 years of age in major depressive disorder and <7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with major depressive disorder or OCD (*see* Pharmacokinetics *under* CLINICAL PHARMACOLOGY).

The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine (*see* ADVERSE REACTIONS).

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the

acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

(*See* WARNINGS, Clinical Worsening and Suicide Risk.)

Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors

(decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

Prozac is approved for use in pediatric patients with MDD and OCD (*see* BOX WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Prozac in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

US fluoxetine clinical trials included 687 patients ≥65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established (*see* CLINICAL TRIALS). For pharmacokinetic information in geriatric patients, see Age under CLINICAL PHARMACOLOGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Prozac, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (*see* PRECAUTIONS, Hyponatremia).

ADVERSE REACTIONS

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 2 enumerates the most common treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US plus non-US controlled trials. Table 3 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US

plus non-US panic disorder controlled clinical trials. Table 3 provides combined data for the pool of studies that are provided separately by indication in Table 2.

Table 2: Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
Body System/ Adverse Event	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence[2]	2	--	--	--	7	--	1	--
Abnormal ejaculation[2]	--	--	7	--	7	--	2	1

[1] Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

[2] Denominator used was for males only (N=690 Prozac major depressive disorder; N=410 placebo major depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia; N=162 Prozac panic; N=121 placebo panic).

-- Incidence less than 1%.

Table 3: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Event[2]	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1
Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

[1] Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.
[2] Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.
-- Incidence less than 1%.

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 4 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Table 4: Most Common Adverse Events Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic Disorder (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

[1] Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Other adverse events in pediatric patients (children and adolescents) — Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 2 and 3. However, the following adverse events (excluding those which appear in the body or footnotes of Tables 2 and 3 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse event (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event associated with discontinuation was collected.

Events observed in Prozac Weekly clinical trials — Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% versus 3%, respectively) or taking Prozac 20 mg daily (10% versus 5%, respectively).

Male and female sexual dysfunction with SSRIs — Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Events Observed in Clinical Trials

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 2 or 3 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient treated with Prozac and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole — *Frequent:* chest pain, chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* acute abdominal syndrome, hypothermia, intentional injury, neuroleptic malignant syndrome[1], photosensitivity reaction.

Cardiovascular System — *Frequent:* hemorrhage, hypertension, palpitation; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System — *Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:* biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional — *Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System — *Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder[2], psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System — *Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses — *Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System — *Frequent:* urinary frequency; *Infrequent:* abortion[3], albuminuria, amenorrhea[3], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation[3], fibrocystic breast[3], hematuria, leukorrhea[3], menorrhagia[3], metrorrhagia[3], nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage[3]; *Rare:* breast engorgement, glycosuria, hypomenorrhea[3], kidney pain, oliguria, priapism[3], uterine hemorrhage[3], uterine fibroids enlarged[3].

[1] Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
[2] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.
[3] Adjusted for gender.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema multiforme,

erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled substance class — Prozac is not a controlled substance.

Physical and psychological dependence — Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was nonlethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience

Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS).

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR).*

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Initial Treatment

Adult — In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

All patients — As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing

Systematic evaluation of Prozac in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see* CLINICAL TRIALS).

Weekly Dosing

Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established (*see* CLINICAL TRIALS).

Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (*see* Weekly dosing *under* CLINICAL PHARMACOLOGY).

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (*see* CLINICAL TRIALS).

Switching Patients to a Tricyclic Antidepressant (TCA)

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS, Drug Interactions).

Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Prozac before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

Obsessive Compulsive Disorder

Initial Treatment

Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials,

adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (*see* CLINICAL TRIALS). Only the 60-mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (*see* CLINICAL TRIALS). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Panic Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in Patients with Concomitant Illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Prozac and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (*see* PRECAUTIONS). When treating pregnant women with Prozac during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Prozac in the third trimester.

Discontinuation of Treatment with Prozac

Symptoms associated with discontinuation of Prozac and other SSRIs and SNRIs, have been reported (*see* PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

HOW SUPPLIED

The following products are manufactured by Eli Lilly and Company for Dista Products Company.

Prozac® Pulvules®, USP, are available in:

The 10-mg[1], Pulvule is opaque green cap and opaque green body, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104[2]) - Bottles of 100

The 20-mg[1] Pulvule is an opaque green cap and opaque yellow body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105[2]) - Bottles of 30
NDC 0777-3105-02 (PU3105[2]) - Bottles of 100
NDC 0777-3105-07 (PU3105[2]) - Bottles of 2000

The 40-mg[1] Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107[2]) - Bottles of 30

The following is manufactured by OSG Norwich Pharmaceuticals, Inc., North Norwich, NY, 13814, for Dista Products Company:

Liquid, Oral Solution is available in:

20 mg[1] per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120[3]) - Bottles of 120 mL

The following product is manufactured and distributed by Eli Lilly and Company:

Prozac® Weekly™ Capsules are available in:

The 90-mg[1] capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) - Blister package of 4

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[1] Fluoxetine base equivalent.
[2] Protect from light.
[3] Dispense in a tight, light-resistant container.

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

ANIMAL TOXICOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

Literature revised January 16, 2008

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.lilly.com

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Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**

2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Patient Information revised June 21, 2007

PV 5083 AMP

Exhibit C3

Search results from the "OB_Rx" table for query on "019268."

Active Ingredient:	MISOPROSTOL
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	CYTOTEC
Applicant:	GD SEARLE LLC
Strength:	0.2MG
Application Number:	019268
Product Number:	001
Approval Date:	Dec 27, 1988
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	MISOPROSTOL
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	CYTOTEC
Applicant:	GD SEARLE LLC
Strength:	0.1MG
Application Number:	019268
Product Number:	003
Approval Date:	Sep 21, 1990
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through September, 2008

Patent and Generic Drug Product Data Last Updated: October 24, 2008

Cytotec®
(misoprostol)

WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (see also **PRECAUTIONS**, and **LABOR AND DELIVERY**). CYTOTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN TO REDUCE THE RISK OF ULCERS INDUCED BY NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (See **CONTRAINDICATIONS**, **WARNINGS** and **PRECAUTIONS**).

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

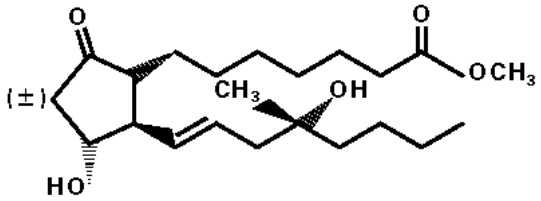
Cytotec should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Cytotec may be prescribed if the patient

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin Cytotec only on the second or third day of the next normal menstrual period.

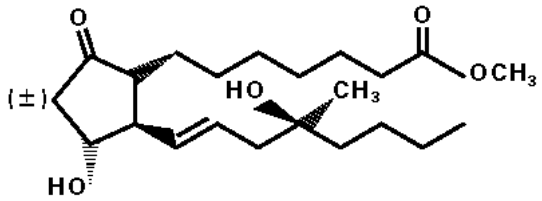
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



And



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11{α}//{alpha}, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Misoprostol is a water-soluble, viscous liquid.

Inactive ingredients of tablets are hydrogenated castor oil, hydroxypropyl methylcellulose, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

In normal volunteers, Cytotec (misoprostol) is rapidly absorbed after oral administration with a T_{max} of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20-40 minutes.

There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important.

Mean ± SD	**C_{max} (pg/ml)**	**AUC(0-4) (pg·hr/ml)**	**T_{max} (min)**
Fasting	811 ± 317	417 ± 135	14 ± 8
With Antacid	689 ± 315	349 ± 108*	20 ± 14
With High Fat Breakfast	303 ± 176*	373 ± 111	64 ± 79*

* Comparisons with fasting results statistically significant, $p<0.05$.

After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max}, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Cytotec does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals.

Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

Pharmacodynamics: Misoprostol has both antisecretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents. Misoprostol can increase bicarbonate and mucus production, but in man this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to reduce the risk of gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.

Effects on gastric acid secretion: Misoprostol, over the range of 50-200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

Uterine effects: Cytotec has been shown to produce uterine contractions that may endanger pregnancy. (See boxed **WARNINGS.**)

Other pharmacologic effects: Cytotec does not produce clinically significant effects on serum levels of prolactin, gonadotropins, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system are not modified by recommended doses of Cytotec.

Clinical studies: In a series of small short-term (about 1 week) placebo-controlled studies in healthy human volunteers, doses of misoprostol were evaluated for their ability to reduce the risk of NSAID-induced mucosal injury. Studies of 200 mcg q.i.d. of misoprostol with tolmetin and naproxen, and of 100 and 200 mcg q.i.d. with ibuprofen, all showed reduction of the rate of significant endoscopic injury from about 70-75% on placebo to 10-30% on misoprostol. Doses of 25-200 mcg q.i.d. reduced aspirin-induced mucosal injury and bleeding.

Reducing the risk of gastric ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs): Two 12-week, randomized, double-blind trials in osteoarthritic patients who had gastrointestinal symptoms but no ulcer on endoscopy while taking an NSAID compared the ability of 200 mcg of Cytotec, 100 mcg of Cytotec, and placebo to reduce the risk of gastric ulcer (GU) formation. Patients were approximately equally divided between ibuprofen, piroxicam, and naproxen, and continued this treatment throughout the 12 weeks. The 200-mcg dose caused a marked, statistically significant reduction in gastric ulcers in both studies. The lower dose was somewhat less effective, with a significant result in only one of the studies.

Reduction of Risk of Gastric Ulcers
Induced by Ibuprofen, Piroxicam, or Naproxen
[No. of patients with ulcer(s) (%)]

Therapy	Therapy Duration			
	4 weeks	8 weeks	12 weeks	
Study No. 1				
Cytotec 200 mcg q.i.d. (n=74)	1(1.4)	0	0	1(1.4)*
Cytotec 100 mcg q.i.d. (n=77)	3(3.9)	1(1.3)	1(1.3)	5(6.5)*
Placebo (n=76)	11(14.5)	4(5.3)	4(5.3)	19(25.0)
Study No. 2				
Cytotec 200 mcg q.i.d. (n=65)	1(1.5)	1(1.5)	0	2(3.1)*
Cytotec 100 mcg q.i.d. (n=66)	2(3.0)	2(3.0)	1(1.5)	5(7.6)
Placebo (n=62)	6(9.7)	2(3.2)	3(4.8)	11(17.7)
*Studies No. 1 & No. 2***				
Cytotec 200 mcg q.i.d. (n=139)	2(1.4)	1(0.7)	0	3(2.2)*
Cytotec 100 mcg q.i.d. (n=143)	5(3.5)	3(2.1)	2(1.4)	10(7.0)*
Placebo (n=138)	17(12.3)	6(4.3)	7(5.1)	30(21.7)

*Statistically significantly different from placebo at the 5% level.
**Combined data from Study No. 1 and Study No. 2.

In these trials there were no significant differences between Cytotec and placebo in relief of day or night abdominal pain. No effect of Cytotec in reducing the risk of duodenal ulcers was demonstrated, but relatively few duodenal lesions were seen.

In another clinical trial, 239 patients receiving aspirin 650-1300 mg q.i.d. for rheumatoid arthritis who had endoscopic evidence of duodenal and/or gastric inflammation were randomized to misoprostol 200 mcg q.i.d. or placebo for 8 weeks while continuing to receive aspirin. The study evaluated the possible interference of Cytotec on the efficacy of aspirin in these patients with rheumatoid arthritis by analyzing joint tenderness, joint swelling, physician's clinical assessment, patient's assessment, change in ARA classification, change in handgrip strength, change in duration of morning stiffness, patient's assessment of pain at rest, movement, interference with daily activity, and ESR. Cytotec did not interfere with the efficacy of aspirin in these patients with rheumatoid arthritis.

INDICATIONS AND USAGE

Cytotec (misoprostol) is indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to reduce the risk of duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to reduce the risk of gastric ulcers in controlled studies of 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed **WARNINGS. Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs).**

Cytotec should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS

See boxed **WARNINGS.**

PRECAUTIONS

Information for patients: Women of childbearing potential using Cytotec to decrease the risk of NSAID induced ulcers should be told that they must not be pregnant when Cytotec therapy is initiated, and they must use an effective contraception method while taking Cytotec.

See boxed **WARNINGS.**

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician.

If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she is or were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: Cytotec may cause abortion (sometimes incomplete), premature labor, or birth defects if given to pregnant women.

Cytotec is available only as a unit-of-use package that includes a leaflet containing patient information. See *Patient Information* at the end of this labeling.

Drug interactions: See *Clinical Pharmacology*. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

Animal toxicology: A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to 1 year.

An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.

Carcinogenesis, mutagenesis, impairment of fertility: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

Pregnancy: Pregnancy Category X.

Teratogenic effects: See boxed **WARNINGS.** Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.

Cytotec in not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

Nonteratogenic effects: **See boxed WARNINGS.** Cytotec may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. Cytotec may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Abortions caused by Cytotec may be incomplete. If a woman is or becomes pregnant while taking this drug to reduce the risk of NSAID induced ulcers, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

Labor and Delivery:

Cytotec can induce or augment uterine contractions. Vaginal administration of Cytotec, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of Cytotec is hyperstimulation of the uterus which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism. Pelvic pain, retained placenta, severe genital bleeding, shock, fetal bradycardia, and fetal and maternal death have been reported.

There may be an increased risk of uterine tachysystole, uterine rupture, meconium passage, meconium staining of amniotic fluid, and Cesarean delivery due to uterine hyperstimulation with the use of higher doses of Cytotec; including the manufactured 100 mcg tablet. The risk of uterine rupture increases with advancing gestational ages and with prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The effect of Cytotec on the later growth, development, and functional maturation of the child when Cytotec is used for cervical ripening or induction of labor have not been established. Information on Cytotec's effect on the need for forceps delivery or other intervention is unknown.

Nursing mothers: It is unlikely that Cytotec is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, Cytotec should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Pediatric use: Safety and effectiveness of Cytotec in pediatric patients have not been established.

ADVERSE REACTIONS

The following have been reported as adverse events in subjects receiving Cytotec:

Gastrointestinal: In subjects receiving Cytotec 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14-40% and in all studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo.

Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of Cytotec with magnesium-containing antacids.

Gynecological: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. (See boxed **WARNINGS.**)

Elderly: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded:

Body as a whole: aches/pains, asthenia, fatigue, fever, rigors, weight changes.

Skin: rash, dermatitis, alopecia, pallor, breast pain.

Special senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.

Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.

Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.

Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.

Hypersensitivity: anaphylaxis

Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.

Genitourinary: polyuria, dysuria, hematuria, urinary tract infection.

Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.

Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.

Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

OVERDOSAGE

The toxic dose of Cytotec in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort being reported. In animals, the acute toxic effects are diarrhea, gastrointestinal lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy.

It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION

The recommended adult oral dose of Cytotec for reducing the risk of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. (See *Clinical Pharmacology: Clinical studies.*) Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.

Renal impairment: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated. (See *Clinical Pharmacology.*)

HOW SUPPLIED

Cytotec 100-mcg tablets are white, round, with SEARLE debossed on one side and 1451 on the other side; supplied as:

NDC Number	Size
0025-1451-60	unit-of-use bottle of 60
0025-1451-20	unit-of-use bottle of 120
0025-1451-34	carton of 100 unit dose

Cytotec 200-mcg tablets are white, hexagonal, with SEARLE debossed above and 1461 debossed below the line on one side and a double stomach debossed on the other side; supplied as:

NDC Number	Size
0025-1461-60	unit-of-use bottle of 60
0025-1461-31	unit-of-use bottle of 100
0025-1461-34	carton of 100 unit dose

Store at or below 25°C (77°F), in a dry area.

Rx only

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (misoprostol) and each time your prescription is renewed, because the leaflet may be changed.

Cytotec (misoprostol) is being prescribed by your doctor to decrease the chance of getting stomach ulcers related to the arthritis/pain medication that you take.

Do not take Cytotec to reduce the risk of NSAID induced ulcers if you are pregnant (See boxed WARNINGS). Cytotec can cause abortion (sometimes incomplete which could lead to dangerous bleeding and require hospitalization and surgery), premature birth, or birth defects. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec has been reported to cause the uterus to rupture (tear) when given after the eighth week of pregnancy. Rupture (tearing) of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death.

If you become pregnant during Cytotec therapy, stop taking Cytotec and contact your physician immediately. Remember that even if you are on a means of birth control it is still possible to become pregnant. Should this occur, stop taking Cytotec and contact your physician immediately.

Cytotec may cause diarrhea, abdominal cramping, and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week. You can minimize possible diarrhea by making sure you take Cytotec with food.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Cytotec. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take Cytotec only according to the directions given by your physician.

Do not give Cytotec to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and would be dangerous if the other person were pregnant.

This information sheet does not cover all possible side effects of Cytotec. This patient information leaflet does not address the side effects of your arthritis/pain medication. See your doctor if you have questions.

Keep out of reach of children.

G.D. Searle & Co.
Box 5110, Chicago IL 60680

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

Exhibit C4

Search results from the "OB_Rx" table for query on "021742."

Active Ingredient:	NEBIVOLOL HYDROCHLORIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	BYSTOLIC
Applicant:	FOREST LABS
Strength:	EQ 2.5MG BASE
Application Number:	021742
Product Number:	002
Approval Date:	Dec 17, 2007
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	NEBIVOLOL HYDROCHLORIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	BYSTOLIC
Applicant:	FOREST LABS
Strength:	EQ 5MG BASE
Application Number:	021742
Product Number:	003
Approval Date:	Dec 17, 2007
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	NEBIVOLOL HYDROCHLORIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	BYSTOLIC
Applicant:	FOREST LABS
Strength:	EQ 10MG BASE
Application Number:	021742
Product Number:	004
Approval Date:	Dec 17, 2007
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through September, 2008

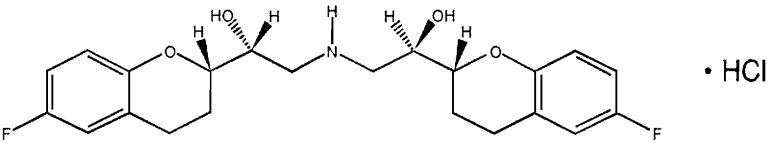
Patent and Generic Drug Product Data Last Updated: October 24, 2008

BYSTOLIC™
(nebivolol) Tablets
2.5 mg, 5 mg and 10 mg

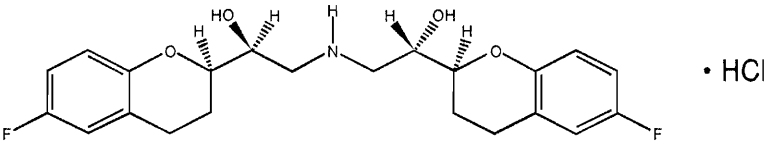
Rx only

DESCRIPTION

The chemical name for the active ingredient in BYSTOLIC (nebivolol) tablets is (1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride. Nebivolol is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol, respectively. Nebivolol's molecular formula is ($C_{22}H_{25}F_2NO_4$•HCl) with the following structural formula:



SRRR - or d-nebivolol hydrochloride



RSSS - or l-nebivolol hydrochloride

MW: 441.90 g/mol

Nebivolol hydrochloride is a white to almost white powder that is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and polyethylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

BYSTOLIC as tablets for oral administration contains nebivolol hydrochloride equivalent to 2.5, 5, and 10 mg of nebivolol base. In addition, BYSTOLIC contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Red #27 Lake, FD&C Blue #2 Lake, FD&C Yellow #6 Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, polysorbate 80, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

General

Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β_1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β_1 and β_2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, BYSTOLIC does not demonstrate α_1-

adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β-blocking activity.

Pharmacodynamics

The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Pharmacokinetics

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity.

Plasma levels of d–nebivolol increase in proportion to dose in EMs and PMs for doses up to 20mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as d-nebivolol's beta receptor affinity is > 1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher Cmax and 10-fold higher AUC of d-nebivolol than do EMs. d-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.

Absorption and Distribution

Absorption of BYSTOLIC is similar to an oral solution. The absolute bioavailability has not been determined.

Mean peak plasma nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing in EMs and PMs.

Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. BYSTOLIC may be administered without regard to meals.

The *in vitro* human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Metabolism and Excretion

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to the pharmacologic activity (see **Drug Interactions**).

After a single oral administration of ^{14}C-nebivolol, 38% of the dose was recovered in urine and 44% in feces for EMs and 67% in urine and 13% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Drug-Interactions
Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When BYSTOLIC is co-administered with an inhibitor or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. *In vitro* studies have demonstrated that at therapeutically relevant concentrations, d- and l-nebivolol do not inhibit any cytochrome P450 pathways.

Digoxin: Concomitant administration of BYSTOLIC (10 mg once daily) and digoxin (0.25 mg once daily) for 10 days in 14 healthy adult individuals resulted in no significant changes in the pharmacokinetics of digoxin or nebivolol (see **PRECAUTION, Drug Interactions**).

Warfarin: Administration of BYSTOLIC (10 mg once daily for 10 days) led to no significant changes in the pharmacokinetics of nebivolol or R- or S-warfarin following a single 10 mg dose of warfarin. Similarly, nebivolol has no significant effects on the anticoagulant activity of warfarin, as assessed by Prothrombin time and INR profiles from 0 to 144 hours after a single 10 mg warfarin dose in 12 healthy adult volunteers.

Diuretics: No pharmacokinetic interactions were observed in healthy adults between nebivolol (10 mg daily for 10 days) and furosemide (40 mg single dose), hydrochlorothiazide (25 mg once daily for 10 days), or spironolactone (25 mg once daily for 10 days).

Ramipril: Concomitant administration of BYSTOLIC (10 mg once daily) and ramipril (5 mg once daily) for 10 days in 15 healthy adult volunteers produced no pharmacokinetic interactions.

Losartan: Concomitant administration of BYSTOLIC (10 mg single dose) and losartan (50 mg single dose) in 20 healthy adult volunteers did not result in pharmacokinetic interactions.

Fluoxetine: Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in Cmax for d-nebivolol (see **PRECAUTIONS, Drug Interactions**).

Histamine-2 Receptor Antagonists: The pharmacokinetics of nebivolol (5 mg single dose) were not affected by the co-administration of ranitidine (150 mg twice daily). Cimetidine (400 mg twice daily) causes a 23% increase in the plasma levels of d-nebivolol.

Charcoal: The pharmacokinetics of nebivolol (10 mg single dose) were not affected by repeated co-administration (4, 8, 12, 16, 22, 28, 36, and 48 hours after nebivolol administration) of activated charcoal (Actidose-Aqua®).

Sildenafil: The co-administration of nebivolol and sildenafil decreased AUC and Cmax of sildenafil by 21 and 23% respectively. The effect on the Cmax and AUC for d -nebivolol was also small (< 20%). The effect on vital signs (e.g., pulse and blood pressure) was approximately the sum of the effects of sildenafil and nebivolol.

Other Concomitant Medications: Utilizing population pharmacokinetic analyses, derived from hypertensive patients, the following drugs were observed not to have an effect on the pharmacokinetics of nebivolol: acetaminophen, acetylsalicylic acid, atorvastatin, esomeprazole, ibuprofen, levothyroxine sodium, metformin, sildenafil, simvastatin, or tocopherol.

Protein Binding: No meaningful changes in the extent of *in vitro* binding of nebivolol to human plasma proteins were noted in the presence of high concentrations of diazepam, digoxin, diphenylhydantoin, enalapril, hydrochlorothiazide, imipramine, indomethacin, propranolol, sulfamethazine, tolbutamide, or warfarin. Additionally, nebivolol did not significantly alter the protein binding of the following drugs: diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations.

Special Populations

Renal Disease: The apparent clearance of nebivolol was unchanged following a single 5 mg dose of BYSTOLIC in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate (ClCr 30 to 50 mL/min, n=9), but by 53% in patients with severe renal impairment (ClCr <30 mL/min, n=5). The dose of BYSTOLIC should be adjusted in patients with severe renal impairment. BYSTOLIC should be used with caution in patients receiving dialysis, since no formal studies have been conducted in this population (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). The starting dose should be reduced in patients with moderate hepatic impairment. No formal studies have been performed in patients with severe hepatic impairment and nebivolol should be contraindicated for these patients (see **DOSAGE AND ADMINISTRATION**).

Clinical Studies

The antihypertensive effectiveness of BYSTOLIC as monotherapy has been demonstrated in three randomized, double-blind, multi-center, placebo-controlled trials at doses ranging from 1.25 to 40 mg for 12 weeks (Studies 1, 2, and 3). A fourth placebo-controlled trial demonstrated additional antihypertensive effects of BYSTOLIC at doses ranging from 5 to 20 mg when administered concomitantly with up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, and thiazide diuretics) in patients with inadequate blood pressure control.

The three monotherapy trials included a total of 2016 patients (1811 BYSTOLIC, 205 placebo) with mild to moderate hypertension who had baseline diastolic blood pressures (DBP) of 95 to 109 mmHg. Patients received either BYSTOLIC or placebo once daily for twelve weeks. Two of these monotherapy trials (Studies 1 and 2) studied 1716 patients in the general hypertensive population with a mean age of 54 years, 55% males, 26% non-Caucasians, 7% diabetics and 6% genotyped as PMs. The third monotherapy trial (Study 3) studied 300 Black

patients with a mean age of 51 years, 45% males, 14% diabetics, and 3% as PMs.

Placebo-subtracted blood pressure reductions by dose for each study are presented in **Table 1**. Most studies showed increasing response to doses above 5 mg.

Table 1. Placebo-Subtracted Least-Square Mean Reductions in Trough Sitting Systolic/Diastolic Blood Pressure (SiSBP/SiDBP mmHg) by Dose in Studies with Once Daily BYSTOLIC

	Nebivolol dose (mg)					
	1.25	2.5	5.0	10	20	30-40
Study 1	-6.6*/-5.1*	-8.5*/-5.6*	-8.1*/-5.5*	-9.2*/-6.3*	-8.7*/-6.9*	-11.7*/-8.3*
Study 2			-3.8/-3.2*	-3.1/-3.9*	-6.3*/-4.5*	
Study 3¶		-1.5/-2.9	-2.6/-4.9*	-6.0*/-6.1*	-7.2*/-6.1*	-6.8*/-5.5*
Study 4^			-5.7*/-3.3*	-3.7*/-3.5*	-6.2*/-4.6*	

* $p<0.05$ based on pair-wise comparison vs placebo
¶ Study enrolled only African Americans.
^ Study on top of one or two other antihypertensive medications.

Study 4 enrolled 669 patients with a mean age of 54 years, 55% males, 54% Caucasians, 29% Blacks, 15% Hispanics, 1% Asians, 14% diabetics, and 5% PMs. BYSTOLIC, 5 mg to 20 mg, administered once daily concomitantly with stable doses of up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, and thiazide diuretics) resulted in significant additional antihypertensive effects over placebo compared to baseline blood pressure.

Effectiveness was similar in subgroups analyzed by age and sex. Effectiveness was established in Blacks, but as monotherapy the magnitude of effect was somewhat less than in Caucasians.

The blood pressure lowering effect of BYSTOLIC was seen within two weeks of treatment and was maintained over the 24-hour dosing interval.

INDICATIONS AND USAGE

BYSTOLIC is indicated for the treatment of hypertension. BYSTOLIC may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

BYSTOLIC is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), or severe hepatic impairment (Child-Pugh >B), and in patients who are hypersensitive to any component of this product.

WARNINGS

Abrupt Cessation of Therapy
Patients with coronary artery disease treated with BYSTOLIC should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Even patients without overt coronary artery disease should be cautioned against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of BYSTOLIC is planned, patients should be carefully observed and advised to minimize physical activity. BYSTOLIC should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that BYSTOLIC be promptly reinstituted, at least temporarily.

Cardiac Failure
Sympathetic stimulation is a vital component supporting circulatory function in the setting of congestive heart failure, and β-blockade may result in further depression of myocardial contractility and precipitate more severe failure. In patients who have compensated congestive heart failure, BYSTOLIC should be administered cautiously. If heart failure worsens, discontinuation of BYSTOLIC should be considered.

Angina and Acute Myocardial Infarction
BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI.

Bronchospastic Diseases
In general, patients with bronchospastic diseases should not receive β-blockers.

Anesthesia and Major Surgery
If BYSTOLIC is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

The β-blocking effects of BYSTOLIC can be reversed by β-agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β-blockers.

Diabetes and Hypoglycemia
β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents,

should be advised about these possibilities and nebivolol should be used with caution.

Thyrotoxicosis

β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Peripheral Vascular Disease

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.

Non-dihydropyridine Calcium Channel Blockers

Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

PRECAUTIONS

Use with CYP2D6 inhibitors

Nebivolol exposure increases with inhibition of CYP2D6 (see **Drug Interactions**). The dose of BYSTOLIC may need to be reduced.

Impaired Renal Function

BYSTOLIC should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis.

Impaired Hepatic Function

BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population (see **CLINICAL PHARMACOLOGY, Special Populations** and **DOSAGE AND ADMINISTRATION**).

Risk of Anaphylactic Reactions

While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

In patients with known or suspected pheochromocytoma, an alpha-blocker should be initiated prior to the use of any β-blocker.

Information for Patients

Patients should be advised to take BYSTOLIC regularly and continuously, as directed. BYSTOLIC can be taken with or without food. If a dose is missed, the patient should take the next scheduled dose only (without doubling it). Patients should not interrupt or discontinue BYSTOLIC without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.

Patients should be advised to consult a physician if any difficulty in breathing occurs, or if they develop signs or symptoms of worsening congestive heart failure such as weight gain or increasing shortness of breath, or excessive bradycardia.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned that β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nebivolol should be used with caution in these patients.

Drug Interactions

BYSTOLIC should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide, are used concurrently. Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

BYSTOLIC should not be combined with other β-blockers. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the added β-blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, BYSTOLIC should be discontinued for several days before the gradual tapering of clonidine.

CYP2D6 Inhibitors: Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) (see **CLINICAL PHARMACOLOGY, Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m^2 basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no

significant effect on ACTH-stimulated mean serum cortisol $AUC_{0\text{-}120\ min}$, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, in vitro mouse lymphoma $TK^{+/-}$, in vitro human peripheral lymphocyte chromosome aberration, in vivo Drosophila melanogaster sex-linked recessive lethal, and in vivo mouse bone marrow micronucleus tests).

Pregnancy: Teratogenic Effects. Pregnancy Category C:
Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Labor and Delivery
Nebivolol caused prolonged gestation and dystocia at doses ≥5 mg/kg in rats (1.2 times the MRHD). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation).

No studies of nebivolol were conducted in pregnant women. BYSTOLIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. It is not known whether this drug is excreted in human milk.

Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended during nursing.

Geriatric Use
Of the 2800 patients in the U.S. sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility (see **Carcinogenesis, Mutagenesis and Impairment of Infertility**).

ADVERSE REACTIONS
The data described below reflect worldwide clinical trial exposure to BYSTOLIC in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received BYSTOLIC for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year. In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse events was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Adverse Reactions in Controlled Trials
Table 2 lists treatment-emergent signs and symptoms that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg or 20-40 mg of BYSTOLIC and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table 2. Treatment-Emergent Adverse Events with an Incidence (over 6 weeks) ≥ 1% in BYSTOLIC-treated Patients and at a Higher Frequency than Placebo-Treated Patients

	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20-40 mg (n = 677) (%)
Headache	6	9	6	7
Fatigue	1	2	2	5
Dizziness	2	2	3	4
Diarrhea	2	2	2	3
Nausea	0	1	3	2
Insomnia	0	1	1	1
Chest pain	0	0	1	1

Bradycardia	0	0	0	1
Dyspnea	0	0	1	1
Rash	0	0	1	1
Peripheral edema	0	1	1	1

Other Adverse Events Observed During Worldwide Clinical Trials
Listed below are other reported adverse events with an incidence of at least 1% in the more than 5300 patients treated with BYSTOLIC in controlled or open-label trials, whether or not attributed to treatment, except for those already appearing in Table 2, terms too general to be informative, minor symptoms, or events unlikely to be attributable to drug because they are common in the population. These adverse events were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a whole: asthenia.

Gastrointestinal System Disorders: abdominal pain

Metabolic and Nutritional Disorders: hypercholesterolemia and hyperuricemia

Nervous System Disorders: paraesthesia

Laboratory
In controlled monotherapy trials, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

Events Identified from Spontaneous Reports of BYSTOLIC Received Worldwide.
The following adverse events have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere. These adverse events have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Events common in the population have generally been omitted. Because these events were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to BYSTOLIC exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

OVERDOSAGE
In clinical trials and worldwide postmarketing experience there were reports of BYSTOLIC overdose. The most common signs and symptoms associated with BYSTOLIC overdosage are bradycardia and hypotension. Other important adverse events reported with BYSTOLIC overdose include cardiac failure,

dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β-blocker overdose include bronchospasm and heart block.

The largest known ingestion of BYSTOLIC worldwide involved a patient who ingested up to 500 mg of BYSTOLIC along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhydrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

If overdose occurs, BYSTOLIC should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other β-blockers, the following general measures should be considered when clinically warranted:

Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Hypotension: Administer IV fluids and vasopressors. Intravenous glucagon may be useful.

Heart Block (second or third degree): Patients should be carefully monitored and treated with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Congestive Heart Failure: Initiate therapy with digitalis glycoside and diuretics. In certain cases, consideration should be given to the use of inotropic and vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled β_2-agonist and/or aminophylline.

Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 12-19 hour effective half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved.

Call the National Poison Control Center (800-222-1222) for the most current information on β-blocker overdose treatment.

DOSAGE AND ADMINISTRATION

The dose of BYSTOLIC should be individualized to the needs of the patient. For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week

intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

Renal Impairment
In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; upward titration should be performed cautiously if needed. BYSTOLIC has not been studied in patients receiving dialysis (see **CLINICAL PHARMACOLOGY, Special Populations**).

Hepatic Impairment
In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; upward titration should be performed cautiously if needed. BYSTOLIC has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population (see **PRECAUTIONS** and **CLINICAL PHARMACOLOGY, Special Populations**).

Geriatric Patients
It is not necessary to adjust the dose in the elderly (see above and **PRECAUTIONS, Geriatric Use**).

CYP2D6 Polymorphism (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**)
No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers.

HOW SUPPLIED
BYSTOLIC is available as tablets for oral administration containing nebivolol hydrochloride equivalent to 2.5, 5, and 10 mg of nebivolol.

BYSTOLIC tablets are triangular-shaped, biconvex, unscored, differentiated by color and are engraved with "**FL**" on one side and the number of mg (2 ½ , 5, or 10) on the other side. BYSTOLIC tablets are supplied in the following strengths and package configurations:

BYSTOLIC			
Tablet Strength	**Package Configuration**	**NDC #**	**Tablet Color**
2.5 mg	Bottle of 30	0456-1402-30	Light Blue
	Bottle of 100	0456-1402-01	
5 mg	Bottle of 30	0456-1405-30	Beige
	Bottle of 100	0456-1405-01	
	10 x 10 Unit Dose	0456-1405-63	
10 mg	Bottle of 30	0456-1410-30	Pinkish -Purple
	Bottle of 100	0456-1410-01	
	10 x 10 Unit Dose	0456-1410-63	

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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Rev. 12/07

Exhibit C5

Search results from the "OB_Rx" table for query on "019810."

Active Ingredient:	OMEPRAZOLE
Dosage Form;Route:	CAPSULE, DELAYED REL PELLETS; ORAL
Proprietary Name:	PRILOSEC
Applicant:	ASTRAZENECA
Strength:	20MG
Application Number:	019810
Product Number:	001
Approval Date:	Sep 14, 1989
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	OMEPRAZOLE
Dosage Form;Route:	CAPSULE, DELAYED REL PELLETS; ORAL
Proprietary Name:	PRILOSEC
Applicant:	ASTRAZENECA
Strength:	40MG
Application Number:	019810
Product Number:	002
Approval Date:	Jan 15, 1998
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	OMEPRAZOLE
Dosage Form;Route:	CAPSULE, DELAYED REL PELLETS; ORAL
Proprietary Name:	PRILOSEC
Applicant:	ASTRAZENECA
Strength:	10MG
Application Number:	019810
Product Number:	003
Approval Date:	Oct 5, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

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Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

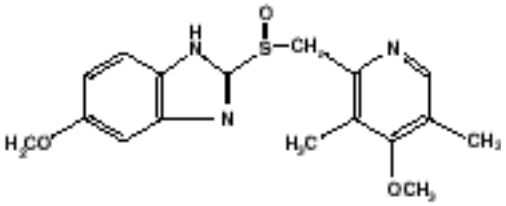
Orange Book Data Updated Through September, 2008

Patent and Generic Drug Product Data Last Updated: October 24, 2008

PRILOSEC®
(OMEPRAZOLE)
DELAYED-RELEASE CAPSULES

DESCRIPTION

The active ingredient in PRILOSEC (omeprazole) Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder that melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

PRILOSEC is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10 mg, 20 mg or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hypromellose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shells have the following inactive ingredients: gelatin-NF, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C Blue #2, D&C Red #7 Calcium Lake, and, in addition, the 10 mg and 40 mg capsule shells also contain D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: Omeprazole

PRILOSEC Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min. Protein binding is approximately 95%.

The bioavailability of omeprazole increases slightly upon repeated administration of PRILOSEC Delayed-Release Capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

When voriconazole (400mg Q12 h x 1 day, then 200mg x 6 days) was given with omeprazole (40 mg once daily x 7 days) to healthy subjects, it significantly increased the steady-state Cmax and AUC 0-24 of omeprazole, an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90%CI: 3.3, 4.4), respectively as compared to when omeprazole was given without voriconazole.

PRILOSEC Delayed-Release Capsule 40 mg was bioequivalent when administered with and without applesauce. However, PRILOSEC Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change in AUC for PRILOSEC Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown.

The pharmacokinetics of omeprazole have been investigated in pediatric patients of different ages.

Pharmacokinetic Parameters of Omeprazole Following Single and Repeated Oral Administration in Pediatric Populations Compared to Adults

Single or Repeated Oral Dosing /Parameter	Children† < 20 kg 2-5 years 10 mg	Children† > 20 kg 6-16 years 20 mg	Adults‡ (mean 76 kg) 23-29 years (n=12)
	Single Dosing		
C_{max}* (ng/mL)	288 (n=10)	495 (n=49)	668
AUC* (ng h/mL)	511 (n=7)	1140 (n=32)	1220
	Repeated Dosing		
C_{max}* (ng/mL)	539 (n=4)	851 (n=32)	1458
AUC* (ng h/mL)	1179 (n=2)	2276 (n=23)	3352

Note: * = plasma concentration adjusted to an oral dose of 1 mg/kg.
†Data from single and repeated dose studies
‡Data from a single and repeated dose study
Doses of 10, 20 and 40 mg Omeprazole as Enteric-Coated Granules

Following comparable mg/kg doses of omeprazole, younger children (2-5 years) have lower AUCs than children 6 – 16 years or adults; AUCs of the latter two groups did not differ. (See DOSAGE AND ADMINISTRATION – Pediatric Patients.)

Pharmacokinetics: Combination Therapy with Antimicrobials

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $T_{1/2}$ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC_{0-8} was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC_{0-8} was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations
2 hours after Dose[1]

Tissue	Clarithromycin	Clarithromycin + Omeprazole
Antrum	10.48 ± 2.01 (n = 5)	19.96 ± 4.71 (n = 5)
Fundus	20.81 ± 7.64 (n = 5)	24.25 ± 6.37 (n = 5)
Mucus	4.15 ± 7.74 (n = 4)	39.29 ± 32.79 (n = 4)

[1] Mean ± SD (µg/g)

For information on clarithromycin pharmacokinetics and microbiology, consult the clarithromycin package insert, CLINICAL PHARMACOLOGY section.

The pharmacokinetics of omeprazole, clarithromycin, and amoxicillin have not been adequately studied when all three drugs are administered concomitantly.

For information on amoxicillin pharmacokinetics and microbiology, see the amoxicillin package insert, ACTIONS, PHARMACOLOGY and MICROBIOLOGY sections.

Pharmacodynamics

Mechanism of Action

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (2-6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies
of the Mean Antisecretory Effects of Omeprazole
After Multiple Daily Dosing

Parameter	Omeprazole 20 mg		Omeprazole 40 mg	
	Max	Min	Max	Min
% Decrease in Basal Acid Output	78*	58-80	94*	80-93
% Decrease in Peak Acid Output	79*	50-59	88*	62-68
% Decrease in 24-hr. Intragastric Acidity		80-97		92-94

* Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies

increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions.) However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans.

However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of PRILOSEC 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also CLINICAL PHARMACOLOGY, Enterochromaffin-like (ECL) Cell Effects).

Clinical Studies

Duodenal Ulcer Disease

Active Duodenal Ulcer— In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg a.m. (n = 99)	Placebo a.m. (n = 48)
Week 2	*41	13
Week 4	*75	27

* ($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with PRILOSEC 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received PRILOSEC had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg a.m. (n = 145)	Ranitidine 150 mg b.i.d. (n = 148)
Week 2	42	34
Week 4	*82	63

* ($p < 0.01$)

Healing occurred significantly faster in patients treated with PRILOSEC than in those treated with ranitidine 150 mg b.i.d. ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of PRILOSEC were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of PRILOSEC were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of PRILOSEC, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg (n = 34)	PRILOSEC 40 mg (n = 36)	Ranitidine 150 mg b.i.d. (n = 35)
Week 2	* 83	* 83	53
Week 4	* 97	*100	82
Week 8	100	100	94

* ($p \leq 0.01$)

H. pylori Eradication in Patients with Duodenal Ulcer Disease

Triple Therapy(PRILOSEC/clarithromycin/amoxicillin)— Three U.S., randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared PRILOSEC plus clarithromycin plus amoxicillin to clarithromycin plus amoxicillin. Two studies (126 and 127) were conducted in patients with an active duodenal ulcer, and the other study (M96-446) was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. The dose regimen in the studies was PRILOSEC 20 mg b.i.d. plus clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days; or clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days. In studies 126 and 127, patients who took the omeprazole regimen also received an additional 18 days of PRILOSEC 20 mg q.d. Endpoints studied were

eradication of *H. pylori* and duodenal ulcer healing (studies 126 and 127 only). *H. pylori* status was determined by CLOtest®, histology and culture in all three studies. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive.

The combination of omeprazole plus clarithromycin plus amoxicillin was effective in eradicating *H. pylori.*

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates
% of Patients Cured [95% Confidence Interval]

	PRILOSEC +clarithromycin +amoxicillin		Clarithromycin +amoxicillin	
	Per-Protocol †	Intent-to-Treat ‡	Per-Protocol †	Intent-to-Treat ‡
Study 126	*77 [64, 86] (n = 64)	*69 [57, 79] (n = 80)	43 [31, 56] (n = 67)	37 [27, 48] (n = 84)
Study 127	*78 [67, 88] (n = 65)	*73 [61, 82] (n = 77)	41 [29, 54] (n = 68)	36 [26, 47] (n = 83)
Study M96-446	*90 [80, 96] (n = 69)	*83 [74, 91] (n = 84)	33 [24, 44] (n = 93)	32 [23, 42] (n = 99)

† Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer, studies 126 and 127; history of ulcer within 5 years, study M96-446) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.

‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.

* ($p < 0.05$) versus clarithromycin plus amoxicillin.

Dual Therapy (PRILOSEC/clarithromycin)— Four randomized, double-blind, multi-center studies (M93-067, M93-100, M92-812b, and M93-058) evaluated PRILOSEC 40 mg q.d. plus clarithromycin 500 mg t.i.d. for 14 days, followed by PRILOSEC 20 mg q.d. (M93-067, M93-100, M93-058) or by PRILOSEC 40 mg q.d. (M92-812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies M93-067 and M93-100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study M93-067 and 228 patients in Study M93-100. These studies compared the combination regimen to PRILOSEC and clarithromycin monotherapies. Studies M92-812b and M93-058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in study M92-812b and 208 patients in Study M93-058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies are described below. *H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated of *H. pylori*. In the per-protocol analysis, the following patients were excluded: dropouts, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication because they were found to have an ulcer at the end of treatment.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori*.

H. pylori Eradication Rates (Per-Protocol Analysis at 4 to 6 Weeks)
% of Patients Cured [95% Confidence Interval]

	PRILOSEC + Clarithromycin	PRILOSEC	Clarithromycin
U.S. Studies			
Study M93-067	74 [60, 85] †‡ (n = 53)	0 [0, 7] (n = 54)	31 [18, 47] (n = 42)
Study M93-100	64 [51, 76] †‡ (n = 61)	0 [0, 6] (n = 59)	39 [24, 55] (n = 44)
Non U.S. Studies			
Study M92-812b	83 [71, 92] ‡ (n = 60)	1 [0, 7] (n = 74)	N/A
Study M93-058	74 [64, 83] ‡ (n = 86)	1 [0, 6] (n = 90)	N/A

† Statistically significantly higher than clarithromycin monotherapy ($p < 0.05$)
‡ Statistically significantly higher than omeprazole monotherapy ($p < 0.05$)

Ulcer healing was not significantly different when clarithromycin was added to omeprazole therapy compared to omeprazole therapy alone.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori* and reduced duodenal ulcer recurrence.

Duodenal Ulcer Recurrence Rates by
H. pylori Eradication Status
% of Patients with Ulcer Recurrence

	H. pylori eradicated#	*H. pylori* not eradicated#
U.S. Studies †		
6 months post-treatment		
Study M93-067	*35 (n = 49)	60 (n = 88)
Study M93-100	*8 (n = 53)	60 (n = 106)
Non U.S. Studies ‡		
6 months post-treatment		
Study M92-812b	*5 (n = 43)	46 (n = 78)
Study M93-058	*6 (n = 53)	43 (n = 107)
12 months post-treatment		
Study M92-812b	*5 (n = 39)	68 (n = 71)

H. pylori eradication status assessed at same timepoint as ulcer recurrence
† Combined results for PRILOSEC + clarithromycin, PRILOSEC, and clarithromycin treatment arms
‡ Combined results for PRILOSEC + clarithromycin and PRILOSEC treatment arms
* ($p \leq 0.01$) versus proportion with duodenal ulcer recurrence who were not *H. pylori* eradicated

Gastric Ulcer

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	PRILOSEC 20 mg q.d. (n = 202)	PRILOSEC 40 mg q.d. (n = 214)	Placebo (n = 104)
Week 4	47.5**	55.6**	30.8
Week 8	74.8**	82.7**,+	48.1

** ($p < 0.01$) PRILOSEC 40 mg or 20 mg versus placebo
+($p < 0.05$) PRILOSEC 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	PRILOSEC 20 mg q.d. (n = 200)	PRILOSEC 40 mg q.d. (n = 187)	Ranitidine 150 mg b.i.d. (n = 199)
Week 4	63.5	78.1**,++	56.3
Week 8	81.5	91.4**,++	78.4

** ($p < 0.01$) PRILOSEC 40 mg versus ranitidine
++ ($p < 0.01$) PRILOSEC 40 mg versus 20 mg

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below.

% Successful Symptomatic Outcome[a]

	PRILOSEC 20 mg a.m.	PRILOSEC 10 mg a.m.	Placebo a.m.
All patients	46*,† (n = 205)	31† (n = 199)	13 (n = 105)
Patients with confirmed GERD	56*,† (n = 115)	36† (n = 109)	14 (n = 59)

[a]Defined as complete resolution of heartburn
*($p < 0.005$) versus 10 mg
†($p < 0.005$) versus placebo

Erosive Esophagitis

In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of PRILOSEC Delayed-Release Capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg PRILOSEC (n = 83)	40 mg PRILOSEC (n = 87)	Placebo (n = 43)
4	39**	45**	7
8	74**	75**	14

** ($p < 0.01$) PRILOSEC versus placebo.

In this study, the 40 mg dose was not superior to the 20 mg dose of PRILOSEC in the percentage healing rate. Other controlled clinical trials have also shown that PRILOSEC is effective in severe GERD. In comparisons with histamine H_2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, PRILOSEC in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with PRILOSEC than in those taking placebo or histamine H_2- receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis

In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose regimens of PRILOSEC were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

Life Table Analysis

	PRILOSEC 20 mg q.d. (n = 138)	PRILOSEC 20 mg 3 days per week (n = 137)	Placebo (n = 131)
Percent in endoscopic remission at 6 months	*70	34	11

*(p < 0.01) PRILOSEC 20 mg q.d. versus PRILOSEC 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, PRILOSEC 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis

	PRILOSEC 20 mg q.d. (n = 131)	PRILOSEC 10 mg q.d. (n = 133)	Ranitidine 150 mg b.i.d. (n = 128)
Percent in endoscopic remission at 12 months	*77	‡58	46

* (p = 0.01) PRILOSEC 20 mg q.d. versus PRILOSEC 10 mg q.d. or Ranitidine.
‡ (p = 0.03) PRILOSEC 10 mg q.d. versus Ranitidine.

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of PRILOSEC was effective, while 10 mg did not demonstrate effectiveness.

Pathological Hypersecretory Conditions

In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PRILOSEC Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). PRILOSEC was well tolerated at these high dose levels for prolonged periods (> 5 years in some patients). In most ZE patients, serum gastrin levels were not modified by PRILOSEC. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 11 patients with ZE syndrome on long-term treatment with PRILOSEC developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of PRILOSEC. (See ADVERSE REACTIONS.)

Microbiology

Omeprazole and clarithromycin dual therapy and omeprazole, clarithromycin and amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Helicobacter
Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest®.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes [a]						
Clarithromycin Pretreatment Results		Clarithromycin Post-treatment Results				
		H. pylori negative - eradicated	*H. pylori* positive - not eradicated Post-treatment susceptibility results			
			S [b]	I [b]	R [b]	No MIC
Dual Therapy - (omeprazole 40 mg q.d./clarithromycin 500 mg t.i.d. for 14 days followed by omeprazole 20 mg q.d. for another 14 days) (Studies M93-067, M93-100)						
Susceptible [b]	108	72	1		26	9
Intermediate [b]	1				1	
Resistant [b]	4				4	
Triple Therapy - (omeprazole 20 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days - Studies 126, 127, M96-446; followed by omeprazole 20 mg q.d. for another 18 days - Studies 126, 127)						
Susceptible [b]	171	153	7		3	8
Intermediate [b]						
Resistant [b]	14	4	1		6	3

[a] Includes only patients with pretreatment clarithromycin susceptibility test results
[b] Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin/amoxicillin triple therapy or omeprazole/clarithromycin dual therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for *Helicobacter pylori*

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs[1]. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard (1 x 10^7 - 1 x 10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar

plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (µg/mL) [a]	Interpretation
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1.0	Resistant (R)

Amoxicillin MIC (µg/mL) [a,b]	Interpretation
≤ 0.25	Susceptible (S)

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (µg/mL) [a]
H. pylori ATCC 43504	Clarithromycin	0.016- 0.12 (µg/mL)
H. pylori ATCC 43504	Amoxicillin	0.016- 0.12 (µg/mL)

[a]These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

INDICATIONS AND USAGE

Duodenal Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori*.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori.*

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY, Clinical Studies and DOSAGE AND ADMINISTRATION).

Among patients who fail therapy, PRILOSEC with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See Microbiology section, and the clarithromycin package insert, MICROBIOLOGY section.)

Gastric Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

PRILOSEC Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis that has been diagnosed by endoscopy.

(See CLINICAL PHARMACOLOGY, Clinical Studies.)

The efficacy of PRILOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

Pathological Hypersecretory Conditions

PRILOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS

Omeprazole

PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

Clarithromycin

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin before prescribing.)

Amoxicillin

Amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. (Please refer to full prescribing information for amoxicillin before prescribing.)

WARNINGS

Clarithromycin

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

Amoxicillin

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.** (See WARNINGS in prescribing information for amoxicillin.)

Antimicrobials

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. (See WARNINGS in prescribing information for clarithromycin and amoxicillin.)

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Information for Patients

PRILOSEC Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

Drug Interactions

Other

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of PRILOSEC.

Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir, thus appropriate clinical monitoring is recommended.

Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Concomitant administration of omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure. Dose adjustment of omeprazole is not normally required. However, in patients with Zollinger-Ellison's syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered. (See Clinical Pharmacology: Pharmacokinetics and Metabolism: Omeprazole).

Combination Therapy with Clarithromycin

Co-administration of omeprazole and clarithromycin has resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics: Combination Therapy with Antimicrobials.)

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated.

There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P450, concomitant administration of clarithromycin with astemizole is not recommended. (See also CONTRAINDICATIONS, Clarithromycin, above. Please refer to full prescribing information for clarithromycin before prescribing.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 57 times the human dose on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

Pregnancy

Omeprazole

Pregnancy Category C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen

Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[2]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[3] *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[4] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[5] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women.

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

Clarithromycin

Pregnancy Category C. See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of PRILOSEC have been established in the age group 2 years to 16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The safety and effectiveness of PRILOSEC have not been established for pediatric patients less than 2 years of age. Use of PRILOSEC in the age group 2 years to 16 years is supported by evidence from adequate and well-controlled studies of PRILOSEC in adults with additional clinical, pharmacokinetic, and safety studies performed in pediatric patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism: Omeprazole).

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In an uncontrolled, open-label study of patients aged 2 years to 16 years with a history of symptoms suggestive of nonerosive GERD, 113 patients were assigned to receive a single daily dose of omeprazole (10 mg or 20 mg, based on body weight) either as an intact capsule or as an open capsule in applesauce. Results showed success rates of 60% (10 mg omeprazole) and 59% (20 mg omeprazole) in reducing the number and intensity of either pain-related symptoms or vomiting/regurgitation episodes.

Erosive Esophagitis

In an uncontrolled, open-label dose-titration study, healing of erosive esophagitis in pediatric patients aged 1 to 16 years required doses that ranged from 0.7 to 3.5 mg/kg/day (80 mg/day). Doses were initiated at 0.7 mg/kg/day. Doses were increased in increments of 0.7 mg/kg/day (if intraesophageal pH showed a pH of < 4 for less than 6% of a 24-hour study). After titration, patients remained on treatment for 3 months. Forty-four percent of the patients were healed on a dose of 0.7 mg/kg body weight; most of the remaining patients were healed with 1.4 mg/kg after an additional 3 months' treatment. Erosive esophagitis was healed in 51 of 57 (90%) children who completed the first course of treatment in the healing phase of the study. In addition, after 3 months of treatment, 33% of the children had no overall symptoms, 57% had mild reflux symptoms, and 40% had less frequent regurgitation/vomiting.

Maintenance of Healing of Erosive Esophagitis

In an uncontrolled, open-label study of maintenance of healing of erosive esophagitis in 46 pediatric patients, 54% of patients required half the healing dose. The remaining patients increased the healing dose (0.7 to a maximum of 2.8 mg/kg/day) either for the entire maintenance period, or returned to half the dose before completion. Of the 46 patients who entered the maintenance phase, 19 (41%) had no relapse. In addition, maintenance therapy in erosive esophagitis patients resulted in 63% of patients having no overall symptoms.

Safety

The safety of PRILOSEC Delayed-Release Capsules has been assessed in 310 pediatric patients aged 0 to 16 years and 62 physiologically normal volunteers aged 2 years to 16 years. Of the 310 pediatric patients with acid-related disease, a group of 46 who had documented healing of erosive esophagitis after 3 months of treatment continued on maintenance therapy for up to 749 days.

PRILOSEC Delayed-Release Capsules administered to pediatric patients was generally well tolerated with an adverse event profile resembling that in adults. Unique to the pediatric population, however, adverse events of the respiratory system were most frequently reported in both the 0 to 2 year and 2 to 16 year age groups (46.2% and 18.5%, respectively). Similarly, otitis media was frequently reported in the 0 to 2 year age group (22.6%), and accidental injuries were reported frequently in the 2 to 16 year age group (3.8%).

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

PRILOSEC Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with PRILOSEC. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions, which occurred in 1% or more of omeprazole-treated patients, have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥ 1%
Causal Relationship not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to PRILOSEC was unclear.

Body As a Whole: Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling
Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema
Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.
Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.
Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain
Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain

Nervous System/Psychiatric: Psychic disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia
Respiratory: Epistaxis, pharyngeal pain
Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, hyperhidrosis
Special Senses: Tinnitus, taste perversion
Ocular: blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis, double vision
Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia
Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Combination Therapy for *H. pylori* Eradication

In clinical trials using either dual therapy with PRILOSEC and clarithromycin, or triple therapy with PRILOSEC, clarithromycin, and amoxicillin, no adverse experiences peculiar to these drug combinations have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with omeprazole, clarithromycin, or amoxicillin.

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin) — The most frequent adverse experiences observed in clinical trials using combination therapy with PRILOSEC, clarithromycin, and amoxicillin (n = 274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking the antimicrobial drugs alone.

For more information on clarithromycin or amoxicillin, refer to the respective package inserts, ADVERSE REACTIONS sections.

Dual Therapy (PRILOSEC/clarithromycin) — Adverse experiences observed in controlled clinical trials using combination therapy with PRILOSEC and clarithromycin (n = 346) which differed from those previously described for omeprazole alone were: Taste perversion (15%), tongue discoloration (2%), rhinitis (2%), pharyngitis (1%) and flu syndrome (1%).

For more information on clarithromycin, refer to the clarithromycin package insert, ADVERSE REACTIONS section.

OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See ADVERSE REACTIONS.) Symptoms were transient, and no serious clinical outcome has been

reported when PRILOSEC was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of PRILOSEC is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

H. pylori Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence

Triple Therapy (PRILOSEC/clarithromycin/amoxicillin) — The recommended adult oral regimen is PRILOSEC 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy (PRILOSEC/clarithromycin) — The recommended adult oral regimen is PRILOSEC 40 mg once daily plus clarithromycin 500 mg t.i.d. for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNING, and for information regarding dosing in elderly and renally impaired patients (PRECAUTIONS: General, PRECAUTIONS: Geriatric Use and PRECAUTIONS: Drug Interactions).

Please refer to amoxicillin full prescribing information for CONTRAINDICATIONS and WARNINGS.

Gastric Ulcer

The recommended adult oral dose is 40 mg once a day for 4 -8 weeks. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer, and INDICATIONS AND USAGE, Gastric Ulcer.)

Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See INDICATIONS AND USAGE.)

Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

Pathological Hypersecretory Conditions

The dosage of PRILOSEC in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRILOSEC for more than 5 years.

Pediatric Patients

For the treatment of GERD or other acid-related disorders, the recommended dose for pediatric patients 2 years of age and older is as follows:

PATIENT WEIGHT	OMEPRAZOLE DOSE
< 20 KG	10 MG
≥ 20 KG	20 MG

ON A PER KG BASIS, THE DOSES OF OMEPRAZOLE REQUIRED TO HEAL EROSIVE ESOPHAGITIS ARE GREATER THAN THOSE FOR ADULTS.

For pediatric patients unable to swallow an intact capsule, see Alternative Administration Options subsection below.

Alternative Administration Options

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

No dosage adjustment is necessary for patients with renal impairment or for the elderly.

PRILOSEC Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with PRILOSEC.

Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

HOW SUPPLIED

No. 3426 — PRILOSEC Delayed-Release Capsules, 10 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 606 on cap and PRILOSEC 10 on the body. They are supplied as follows:

NDC 0186-0606-31 unit of use bottles of 30

NDC 0186-0606-82 bottles of 1000.

No. 3440 — PRILOSEC Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules, coded 742 on cap and PRILOSEC 20 on body. They are supplied as follows:

NDC 0186-0742-31 unit of use bottles of 30
NDC 0186-0742-82 bottles of 1000.

No. 3428 — PRILOSEC Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 743 on cap and PRILOSEC 40 on the body. They are supplied as follows:

NDC 0186-0743-31 unit of use bottles of 30
NDC 0186-0743-68 bottles of 100
NDC 0186-0743-82 bottles of 1000.

Storage

Store PRILOSEC Delayed-Release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F and 86°F).

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol, 20, No. 2, NCCLS, Wayne, PA, January 2000.

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3. Kallen BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001;96(1):63-8.

4. Ruidómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150:476-81.

5. Lalkin A, Loebstein R, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998;179:727-30.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

91941XX
31090-XX
10/06

AstraZeneca

Exhibit C6

Search results from the "OB_Rx" table for query on "017577."

Active Ingredient:	OXYBUTYNIN CHLORIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	DITROPAN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	5MG
Application Number:	017577
Product Number:	001
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

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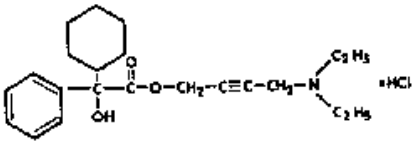
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2008
Patent and Generic Drug Product Data Last Updated: October 24, 2008

DITROPAN®
(oxybutynin chloride)
Tablets and Syrup

DESCRIPTION

Each scored biconvex, engraved blue DITROPAN® (oxybutynin chloride) Tablet contains 5 mg of oxybutynin chloride. Each 5 mL of DITROPAN Syrup contains 5 mg of oxybutynin chloride. Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \bullet HCl$. The structural formula appears below:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

DITROPAN Tablets also contain calcium stearate, FD&C Blue #1 Lake, lactose, and microcrystalline cellulose.

DITROPAN Syrup also contains citric acid, FD&C Green #3, glycerin, methylparaben, flavor, sodium citrate, sorbitol, sucrose, and water.

DITROPAN Tablets and Syrup are for oral administration.

Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominately in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Following oral administration of DITROPAN, oxybutynin is rapidly absorbed achieving C_{max} within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. The absolute bioavailability of oxybutynin is reported to be about 6% (range 1.6 to 10.9%) for both the tablet and syrup. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin.

The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1 Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following Three Doses of DITROPAN 5 mg Administered every 8 Hours (n=23)

Parameters (units)	R-Oxybutynin	S-Oxybutynin
C_{max} (ng/mL)	3.6 (2.2)	7.8 (4.1)
T_{max} (h)	0.89 (0.34)	0.65 (0.32)
AUC_t (ng·h/mL)	22.6 (11.3)	35.0 (17.3)
AUC_{inf} (ng·h/mL)	24.3 (12.3)	37.3 (18.7)

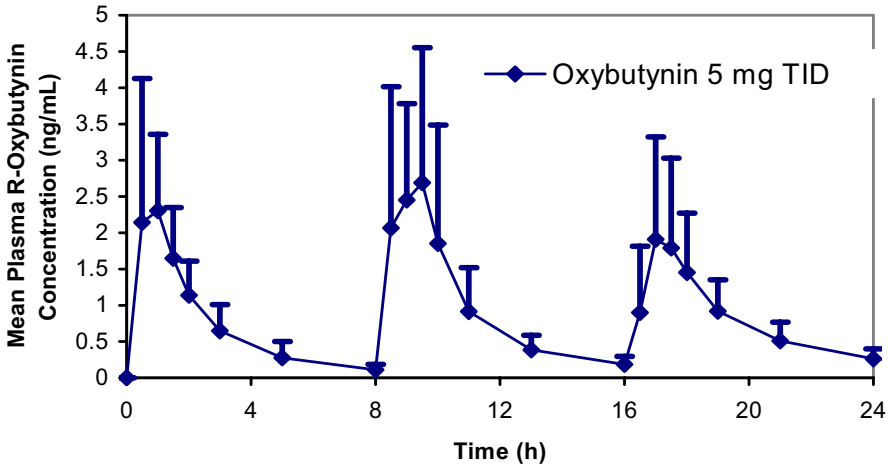


Figure 1. Mean R-oxybutynin plasma concentrations following three doses of DITROPAN 5 mg administered every 8 hours for 1 day in 23 healthy adult volunteers

DITROPAN steady-state pharmacokinetics were also studied in 23 pediatric patients with detrusor overactivity associated with a neurological condition (e.g., spina bifida). These pediatric patients were on DITROPAN tablets (n=11) with total daily dose ranging from 7.5 mg to 15 mg (0.22 to 0.53 mg/kg) or DITROPAN syrup (n=12) with total daily dose ranging from 5 mg to 22.5 mg (0.26 to 0.75 mg/kg). Overall, most patients (86.9%) were taking a total daily DITROPAN dose between 10 mg and 15 mg. Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg twice daily DITROPAN, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2a (for tablet) and Table 2b (for syrup). The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg twice daily.

Table 2a Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of DITROPAN Tablets (N=11)

All Available Data Normalized to an Equivalent of DITROPAN Tablets 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}* (ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

Table 2b Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 5 mg to 22.5 mg Total Daily Dose of DITROPAN Syrup (N=12)

All Available Data Normalized to an Equivalent of DITROPAN Syrup 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}* (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

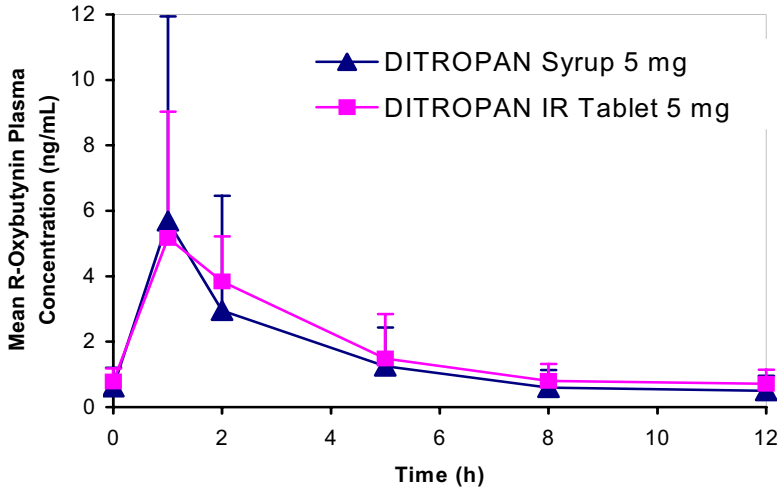


Figure 2. Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of total daily DITROPAN dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age. – Plot represents all available data normalized to the equivalent of DITROPAN 5 mg BID or TID at steady state

Food Effects

Data in the literature suggests that oxybutynin solution co-administered with food resulted in a slight delay in absorption and an increase in its bioavailability by 25% (n=18). [1]

Distribution

Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

CLINICAL STUDIES

DITROPAN was well tolerated in patients administered the drug in controlled studies of 30 days' duration and in uncontrolled studies in which some of the patients received the drug for 2 years.

INDICATIONS AND USAGE

DITROPAN® (oxybutynin chloride) is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

DITROPAN® (oxybutynin chloride) is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

Central Nervous System Effects

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects (See **ADVERSE REACTIONS**). A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

DITROPAN should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

General

DITROPAN® (oxybutynin chloride) should be used with caution in the frail elderly, in patients with hepatic or renal impairment, and in patients with myasthenia gravis.

DITROPAN may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, myasthenia gravis, and prostatic hypertrophy.

Urinary Retention

DITROPAN should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders

DITROPAN should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Administration of DITROPAN to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

DITROPAN, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, and intestinal atony.

DITROPAN should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence), or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 3-4 fold higher when DITROPAN was administered with ketoconazole, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy

Category B. Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN administered to women who are or who may become pregnant has not been established. Therefore, DITROPAN should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN is administered to a nursing woman.

Pediatric Use

The safety and efficacy of DITROPAN administration have been demonstrated for pediatric patients 5 years of age and older (see **DOSAGE AND ADMINISTRATION**).

The safety and efficacy of DITROPAN Tablets and DITROPAN Syrup were studied in 30 and in 26 children, respectively, in a 24-week, open-label trial. Patients were aged 5-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that the administration of DITROPAN was associated with improvement in clinical and urodynamic parameters.

At total daily doses ranging from 5 mg to 15 mg, treatment with DITROPAN Tablets was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%. Urodynamic results in these patients were consistent with the clinical results. Treatment with DITROPAN Tablets was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H_20 to 33 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 39% to 20%.

At total daily doses ranging from 5 mg to 30 mg, treatment with DITROPAN Syrup was associated with an increase from baseline in mean urine volume per catheterization from 113 mL to 133 mL, an increase from baseline in mean urine volume after morning awakening from 143 mL to 165 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 63%. Urodynamic results were consistent with these clinical results. Treatment with DITROPAN Syrup was associated with an increase from baseline in maximum cystometric capacity from 192 mL to 294 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 cm H20 to 37 cm H20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 67% to 28%.

As there is insufficient clinical data for pediatric populations under age 5, DITROPAN is not recommended for this age group.

Geriatric Use

Clinical studies of DITROPAN did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between healthy elderly and younger patients; however, a lower initial starting dose of 2.5 mg

given 2 or 3 times a day has been recommended for the frail elderly due to a prolongation of the elimination half-life from 2-3 hours to 5 hours.[2, 3, 4] In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety and efficacy of DITROPAN® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials comparing DITROPAN with DITROPAN XL (see Table 3). These participants were treated with DITROPAN 5-20 mg/day for up to 6 weeks. Table 3 shows the incidence of adverse events judged by investigators to be at least possibly related to treatment and reported by at least 5% of patients.

Table 3 Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN (5-20 mg/day)

Body System	Adverse Event	DITROPAN (5-20 mg/day) (n=199)
Infections and Infestations	Urinary tract infection	6.5%
Psychiatric Disorders	Insomnia	5.5%
	Nervousness	6.5%
Nervous System Disorders	Dizziness	16.6%
	Somnolence	14.0%
	Headache	7.5%
Eye Disorders	Blurred vision	9.6%
Gastrointestinal Disorders	Dry mouth	71.4%
	Constipation	15.1%
	Nausea	11.6%
	Dyspepsia	6.0%
Renal and Urinary Disorders	Urinary Hesitation	8.5%
	Urinary Retention	6.0%

The most common adverse events reported by patients receiving DITROPAN 5-20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 1 to <5% of patients using DITROPAN (5-20 mg/day) in all studies. *Infections and Infestations*: nasopharyngitis, upper respiratory tract infection, bronchitis, cystitis, fungal infection; *Metabolism and Nutrition Disorders*: fluid retention; *Psychiatric Disorders*: confusional state; *Nervous System Disorders*: dysgeusia, sinus headache; *Eye Disorders*: keratoconjunctivitis sicca, eye irritation; *Cardiac Disorders*: palpitations, sinus arrhythmia; *Vascular Disorders*: flushing; *Respiratory, Thoracic and Mediastinal Disorders*: nasal dryness, cough, pharyngolaryngeal pain, dry throat, sinus congestion, hoarseness, asthma, nasal congestion; *Gastrointestinal Disorders*:

diarrhea, abdominal pain, loose stools, flatulence, vomiting, abdominal pain upper, dysphagia, aptyalism, eructation, tongue coated; *Skin and Subcutaneous Tissue Disorders*: dry skin, pruritis; *Musculoskeletal and Connective Tissue Disorders*: back pain, arthralgia, pain in extremity, flank pain; *Renal and Urinary Disorders*: dysuria, pollakiuria; *General Disorders and Administration Site Conditions*: fatigue, edema peripheral, asthenia, pain, thirst, edema; *Investigations*: blood pressure increased, blood glucose increased, blood pressure decreased; *Injury, Poisoning, and Procedural Complications*: fall.

Postmarketing Surveillance

Because postmarketing adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse events have been reported from worldwide postmarketing experience with DITROPAN: *Psychiatric Disorders*: psychotic disorder, agitation, hallucinations; *Nervous System Disorders*: convulsions; *Eye disorders*: cycloplegia, mydriasis; *Cardiac Disorders*: tachycardia; *Gastrointestinal Disorders*: decreased gastrointestinal motility; *Skin and Subcutaneous Tissue Disorders*: rash, decreased sweating; *Renal and Urinary Disorders*: impotence; *Reproductive system and breast disorders*: Suppression of lactation.

OVERDOSAGE

Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Other symptoms may include hypotension or hypertension, respiratory failure, paralysis, and coma.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

Tablets

Adults: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day.

Syrup

Adults: The usual dose is one teaspoon (5 mg/5 mL) of syrup two to three times a day. The maximum recommended dose is one teaspoon (5 mg/5 mL) of syrup four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one teaspoon (5 mg/5 mL) of syrup two times a day. The maximum recommended dose is one teaspoon (5 mg/5mL) of syrup three times a day.

HOW SUPPLIED

DITROPAN® (oxybutynin chloride) Tablets are supplied in bottles of 100 tablets (NDC 17314-9200-1). Blue scored tablets (5 mg) are engraved with DITROPAN on one side with 92 and 00, separated by a horizontal score, on the other side.

DITROPAN Syrup (5 mg/5 mL) is supplied in bottles of 16 fluid ounces (473 mL) (NDC 17314-9201-4).

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.
Store at controlled room temperature 59-86°F (15-30°C).

REFERENCES

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4. Yarker Y et al. Oxybutynin: A review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging.* 1995; 6(3): 243-262.

RX ONLY

Manufactured by sanofi-aventis U.S. LLC, Kansas City, MO 64137.

Distributed and Marketed by Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ 08869

(OMP Logo)

Revised February 2008

50070622
633-20-616-X

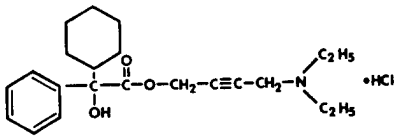
DITROPAN XL®
(oxybutynin chloride)
Extended Release Tablets

DESCRIPTION

DITROPAN XL® (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each DITROPAN XL Extended Release Tablet contains 5 mg, 10 mg, or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S-enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \bullet HCl$.

Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

DITROPAN XL also contains the following inert ingredients: cellulose acetate, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

System Components and Performance

DITROPAN XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the

rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of DITROPAN XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Following the first dose of DITROPAN XL® (oxybutynin chloride), oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from DITROPAN XL are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1 **Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of DITROPAN XL 10 mg (n=43)**

Parameters (units)	R-Oxybutynin		S-Oxybutynin	
C_{max} (ng/mL)	1.0	(0.6)	1.8	(1.0)
T_{max} (h)	12.7	(5.4)	11.8	(5.3)
$t_{1/2}$ (h)	13.2	(6.2)	12.4	(6.1)
$AUC_{(0-48)}$ (ng·h/mL)	18.4	(10.3)	34.2	(16.9)
AUC_{inf} (ng·h/mL)	21.3	(12.2)	39.5	(21.2)

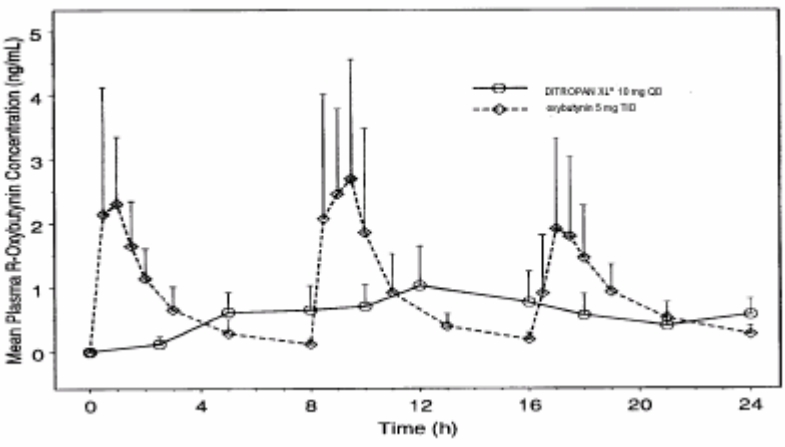


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of DITROPAN XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated DITROPAN XL dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

DITROPAN XL steady-state pharmacokinetics were studied in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g. spina bifida). The children were on DITROPAN XL total daily dose ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg per day DITROPAN XL, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

Table 2 **Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20 mg DITROPAN XL Once Daily (n=19) All Available Data Normalized to an Equivalent of DITROPAN XL 5 mg Once Daily**

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max} (ng/mL)	0.7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4.2 ± 2.3
T_{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng·hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

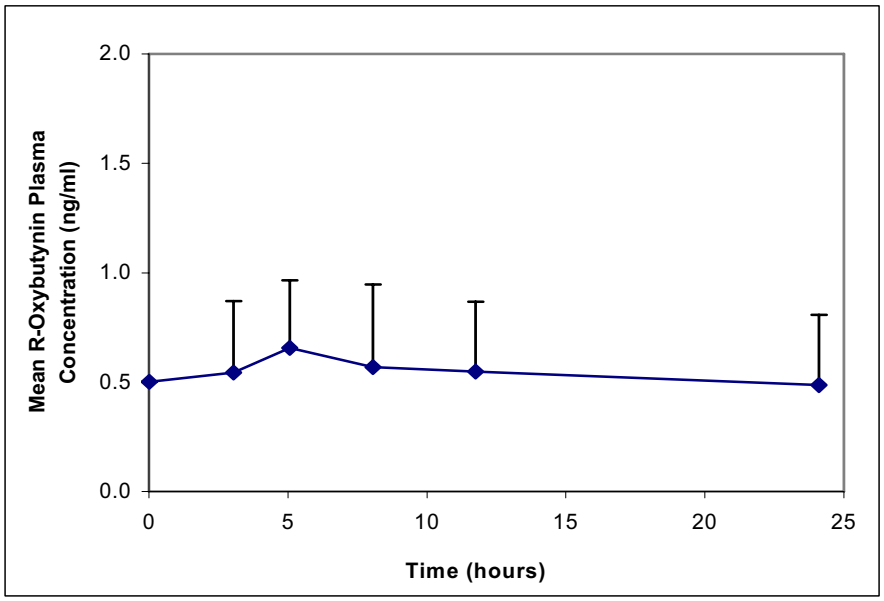


Figure 2. Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg DITROPAN XL once daily in children aged 5-15. Plot represents all available data normalized to an equivalent of DITROPAN XL 5 mg once daily.

Food Effects

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution

Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following DITROPAN XL

administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of DITROPAN XL are dose proportional.

Special Populations

Geriatric:

The pharmacokinetics of DITROPAN XL were similar in all patients studied (up to 78 years of age).

Pediatric:

The pharmacokinetics of DITROPAN XL were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of DITROPAN XL in these pediatric patients were consistent with those reported for adults (see Tables 1 and 2, and Figures 1 and 2 above).

Gender:

There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of DITROPAN XL.

Race:

Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of DITROPAN XL.

Renal Insufficiency:

There is no experience with the use of DITROPAN XL in patients with renal insufficiency.

Hepatic Insufficiency:

There is no experience with the use of DITROPAN XL in patients with hepatic insufficiency.

Drug-Drug Interactions:
See **PRECAUTIONS:** Drug Interactions.

CLINICAL STUDIES

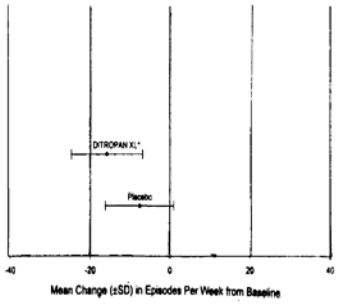
DITROPAN XL® (oxybutynin chloride) was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a fixed dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

The efficacy results for the three controlled trials are presented in the following tables and figures.

Number of Urge Urinary Incontinence Episodes Per Week

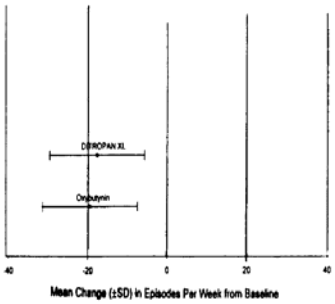
Study 1	N	DITROPAN® XL	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – Placebo)		(-13.6, -2.8)*		

* The difference between DITROPAN® XL and placebo was statistically significant.
† Covariate adjusted mean with missing observations set to baseline values



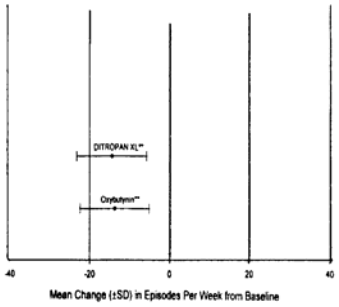
Study 2	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-2.8, 6.5)		

† Covariate adjusted mean with missing observations set to baseline values



Study 3	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline†	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-3.0, 1.6)**		

** The difference between DITROPAN® XL and oxybutynin fulfilled the criteria for comparable efficacy.
† Covariate adjusted mean with missing observations set to baseline values



INDICATIONS AND USAGE

DITROPAN XL® (oxybutynin chloride) is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

DITROPAN XL is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

CONTRAINDICATIONS

DITROPAN XL® (oxybutynin chloride) is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN XL is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

Central Nervous System Effects

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects (See **ADVERSE REACTIONS**). A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

DITROPAN XL should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

General

DITROPAN XL® (oxybutynin chloride) should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention

DITROPAN XL should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders

DITROPAN XL should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

DITROPAN XL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

DITROPAN XL should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering DITROPAN XL to patients with preexisting severe gastrointestinal

narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that DITROPAN XL should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

DITROPAN XL should be taken at approximately the same time each day.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when DITROPAN XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN XL should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN XL is administered to a nursing woman.

Pediatric Use

The safety and efficacy of DITROPAN XL were studied in 60 children in a 24-week, open-label trial. Patients were aged 6-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that administration of DITROPAN XL 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results were consistent with clinical results. Administration of DITROPAN XL resulted in an increase from baseline in mean maximum cystometric

capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

DITROPAN XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (See **DOSAGE AND ADMINISTRATION**).

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations:** ~~Gender~~ Geriatric).

ADVERSE REACTIONS

Adverse Events with DITROPAN XL

The safety and efficacy of DITROPAN XL® (oxybutynin chloride) was evaluated in a total of 580 participants who received DITROPAN XL in 4 clinical trials (429 patients) and four pharmacokinetic studies (151 healthy volunteers). The 429 patients were treated with 5-30 mg/day for up to 4.5 months. Three of the 4 clinical trials allowed dose adjustments based on efficacy and adverse events and one was a fixed dose escalation design. Safety information is provided for 429 patients from these three controlled clinical studies and one open label study in the first column of Table 3 below.

Adverse events from two additional fixed dose, active controlled, 12 week treatment duration, postmarketing studies, in which 576 patients were treated with DITROPAN XL 10 mg/day, are also listed in Table 3 (second column). The adverse events are reported regardless of causality.

Table 3 Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN XL (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10mg/day) Studies

Body System	Adverse Event	DITROPAN XL 5-30 mg/day (n=429)	DITROPAN XL 10 mg/day (n=576)
General	headache	10	6
	asthenia	7	3
	pain	7	4
Digestive	dry mouth	61	29
	constipation	13	7
	diarrhea	9	7
	nausea	9	2
	dyspepsia	7	5
Nervous	somnolence	12	2
	dizziness	6	4
Respiratory	rhinitis	6	2
Special senses	blurred vision	8	1
	dry eyes	6	3
Urogenital	urinary tract infection	5	5

The most common adverse events reported by the 429 patients receiving 5-30 mg/day DITROPAN XL were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8% in the 429 patients from the 4 studies of efficacy and safety who received 5-30 mg/day. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by ≥1 to < 5% of all patients who received DITROPAN XL in the 6 adjustable and fixed dose efficacy and safety studies. *Infections and infestations*: nasopharyngitis, upper respiratory tract infection, sinusitis, bronchitis, cystitis; *Psychiatric disorders*: insomnia, depression, nervousness, confusional state; *Nervous System Disorders*: dysgeusia; *Cardiac disorders*: palpitations; *Vascular disorders*: hypertension; *Respiratory, thoracic and mediastinal disorders*: nasal dryness, cough, pharyngolaryngeal pain, dry throat; *Gastrointestinal Disorders*: gastroesophageal reflux disease, abdominal pain, loose stools, flatulence, vomiting; *Skin and subcutaneous tissue disorders*: dry skin, pruritis; *Musculoskeletal and connective tissue disorders*: back pain, arthralgia, pain in extremity; *Renal and urinary disorders*: urinary retention, urinary hesitation, dysuria; *General disorders and administration site conditions*: fatigue, edema peripheral, asthenia, chest pain; *Investigations*: blood pressure increased.

Postmarketing Surveillance

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse drug reactions have been reported from worldwide postmarketing experience with DITROPAN XL: *Psychiatric Disorders*: psychotic disorder, agitation, hallucinations; *Nervous System Disorders*: convulsions; *Cardiac Disorders*: arrhythmia; tachycardia; *Vascular Disorders*: flushing; *Skin and Subcutaneous Tissue Disorders*: rash; *Renal and Urinary Disorders*: impotence; *Injury, poisoning and procedural complications*: fall.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

OVERDOSAGE

The continuous release of oxybutynin from DITROPAN XL® (oxybutynin chloride) should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

DITROPAN XL® (oxybutynin chloride) must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

DITROPAN XL may be administered with or without food.

Adults:

The recommended starting dose of DITROPAN XL is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric Patients Aged 6 Years of Age and Older:

The recommended starting dose of DITROPAN XL is 5 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

DITROPAN XL® (oxybutynin chloride) Extended Release Tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink), and 15 mg (gray) and are imprinted with "5 XL", "10 XL", or "15 XL". DITROPAN XL Extended Release Tablets are supplied in bottles of 100 tablets.

5 mg	100 count bottle	NDC 17314-8500-1
10 mg	100 count bottle	NDC 17314-8501-1
15 mg	100 count bottle	NDC 17314-8502-1

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and humidity.

Rx Only

For more information call 1-888-395-1232 or visit www.DITROPANXL.com

Manufactured by
ALZA Corporation, Mountain View, CA 94043

Placeholder for ALZA Corporation Logo

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Technology Product

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631-10-800-X

Revised February 2008

Exhibit C7

Search results from the "OB_Rx" table for query on "020281."

Active Ingredient:	TRAMADOL HYDROCHLORIDE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ULTRAM
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	50MG
Application Number:	020281
Product Number:	002
Approval Date:	Mar 3, 1995
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

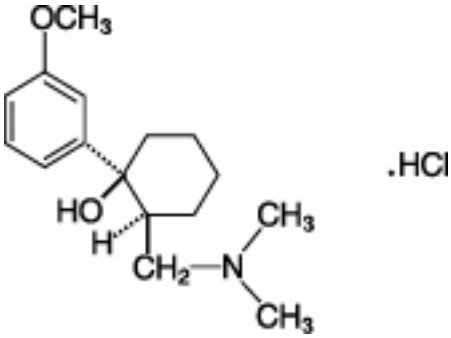
Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2008
Patent and Generic Drug Product Data Last Updated: October 24, 2008

ULTRAM® (tramadol hydrochloride tablets)

DESCRIPTION

ULTRAM® (tramadol hydrochloride tablets) is a centrally acting analgesic. The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. ULTRAM tablets contain 50 mg of tramadol hydrochloride and are white in color. Inactive ingredients in the tablet are corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax.

CLINICAL PHARMACOLOGY

Pharmacodynamics

ULTRAM is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of ULTRAM. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

Apart from analgesia, ULTRAM administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, ULTRAM has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacokinetics

The analgesic activity of ULTRAM is due to both parent drug and the M1 metabolite (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Tramadol is administered as a racemate and both the [-] and

[+] forms of both tramadol and M1 are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. Tramadol has a volume of distribution of approximately 2.7L/kg and is only 20% bound to plasma proteins. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. The formation of M1 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS, Drug Interactions). Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption:
Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~ 10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with q.i.d. dosing. There is no evidence of self-induction (see Figure 1 and Table 1 below).

Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given q.i.d.

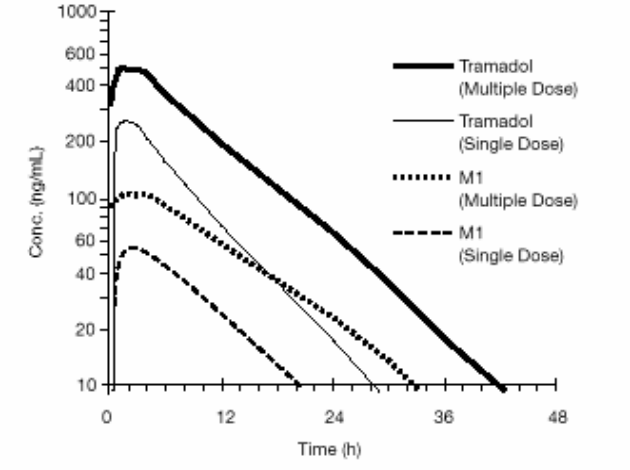


Table 1
Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/ Dosage Regimen[a]	Parent Drug/ Metabolite	Peak Conc. (ng/mL)	Time to Peak (hrs)	Clearance/F[b] (mL/min/Kg)	$t_{1/2}$ (hrs)
Healthy Adults, 100 mg qid, MD p.o.	Tramadol	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
	M1	110 (29)	2.4 (46)	c	7.0 (14)
Healthy Adults, 100 mg SD p.o.	Tramadol	308 (25)	1.6 (63)	8.50 (31)	5.6 (20)
	M1	55.0 (36)	3.0 (51)	c	6.7 (16)
Geriatric, (>75 yrs) 50 mg SD p.o.	Tramadol	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
	M1	d	d	c	d
Hepatic Impaired, 50 mg SD p.o.	Tramadol	217 (11)	1.9 (16)	4.23 (56)	13.3 (11)
	M1	19.4 (12)	9.8 (20)	c	18.5 (15)
Renal Impaired, CL_{cr}10-30 mL/min 100 mg SD i.v.	Tramadol	c	c	4.23 (54)	10.6 (31)
	M1	c	c	c	11.5 (40)
Renal Impaired, CL_{cr}<5 mL/min 100 mg SD i.v.	Tramadol	c	c	3.73 (17)	11.0 (29)
	M1	c	c	c	16.9 (18)

a SD = Single dose, MD = Multiple dose, p.o.= Oral administration, i.v.= Intravenous administration, q.i.d. = Four times daily
b F represents the oral bioavailability of tramadol
c Not applicable
d Not measured

Food Effects: Oral administration of ULTRAM with food does not significantly affect its rate or extent of absorption, therefore, ULTRAM can be administered without regard to food.

Distribution:
The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism:
Tramadol is extensively metabolized after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. One metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS, Drug Interaction).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of

SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

Elimination:
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing.

Special Populations

Renal:
Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic:
Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION).

Geriatric:
Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see DOSAGE AND ADMINISTRATION).

Gender:
The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

Clinical Studies

ULTRAM has been given in single oral doses of 50, 75 and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).

In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg ULTRAM tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.

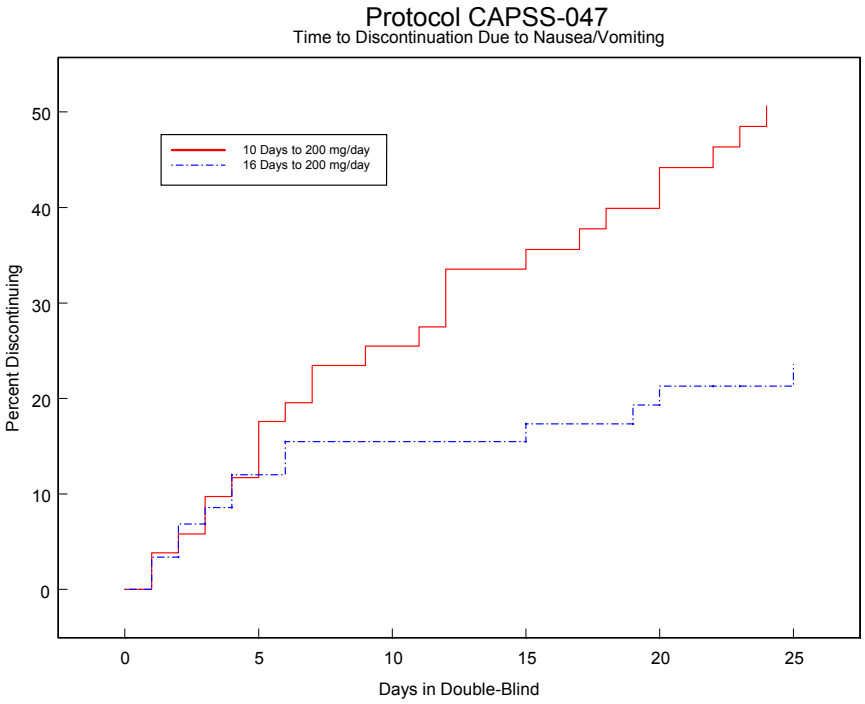
ULTRAM has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving ULTRAM. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of ULTRAM in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL® with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX®) daily.

Titration Trials

In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate ULTRAM therapy using slower titration rates.

A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule.

Figure 2:



INDICATIONS AND USAGE

ULTRAM is indicated for the management of moderate to moderately severe pain in adults.

CONTRAINDICATIONS

ULTRAM should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. ULTRAM is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRAM may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving ULTRAM within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of ULTRAM

above the recommended range. Concomitant use of ULTRAM increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of ULTRAM may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In ULTRAM overdose, naloxone administration may increase the risk of seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with ULTRAM. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRAM (see CONTRAINDICATIONS).

Respiratory Depression

Administer ULTRAM cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of ULTRAM are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS, Seizure Risk and OVERDOSAGE).

Interaction With Central Nervous System (CNS) Depressants

ULTRAM should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. ULTRAM increases the risk of CNS and respiratory depression in these patients.

Increased Intracranial Pressure or Head Trauma

ULTRAM should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRAM. (See Respiratory Depression.)

Use in Ambulatory Patients

ULTRAM may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors

Use ULTRAM with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of ULTRAM with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Withdrawal

Withdrawal symptoms may occur if ULTRAM is discontinued abruptly. (See DRUG ABUSE AND DEPENDENCE.) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with ULTRAM discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering ULTRAM at the time of discontinuation.

Physical Dependence and Abuse

ULTRAM may induce psychic and physical dependence of the morphine-type (μ-opioid) (see DRUG ABUSE AND DEPENDENCE). ULTRAM should not be used in opioid-dependent patients. ULTRAM has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.

Risk of Overdosage

Serious potential consequences of overdosage with ULTRAM (tramadol hydrochloride tablets) are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see OVERDOSAGE).

PRECAUTIONS

Acute Abdominal Conditions

The administration of ULTRAM may complicate the clinical assessment of patients with acute abdominal conditions.

Use in Renal and Hepatic Disease

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION).
With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

Information for Patients

- ULTRAM may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- ULTRAM should not be taken with alcohol containing beverages.
- ULTRAM should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see PRECAUTIONS, Labor and Delivery).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures and death.

Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Use With Carbamazepine
Patients taking **carbamazepine** may have a significantly reduced analgesic effect of ULTRAM. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of ULTRAM and carbamazepine is not recommended.

Use With Quinidine
Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and ULTRAM results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use With Inhibitors of CYP2D6
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use With Cimetidine
Concomitant administration of ULTRAM with **cimetidine** does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRAM dosage regimen is recommended.

Use With MAO Inhibitors
Interactions with **MAO Inhibitors**, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use With MAO Inhibitors).

Use With Digoxin and Warfarin
Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.36 times the maximum daily human dosage of 246 mg/m^2) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 0.73 times the maximum daily human dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m^2, respectively.

Pregnancy, Teratogenic Effects: *Pregnancy Category C*

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m^2), rats (≥25 mg/kg or 150 mg/m^2) and rabbits (≥75 mg/kg or 900 mg/m^2) at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages on a mg/m^2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m^2) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m^2), rats (up to 80 mg/kg or 480 mg/m^2) or rabbits (up to 300 mg/kg or 3600 mg/m^2) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m^2), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m^2), respectively.

Non-teratogenic Effects
Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/ m^2 or 1.2 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 1.9 and higher the maximum daily human dose).

There are no adequate and well-controlled studies in pregnant women. ULTRAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

Labor and Delivery

ULTRAM should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see DRUG ABUSE AND DEPENDENCE). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRAM, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours postdose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

Pediatric Use

The safety and efficacy of ULTRAM in patients under 16 years of age have not been established. The use of ULTRAM in the pediatric population is not recommended.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

A total of 455 elderly (65 years of age or older) subjects were exposed to ULTRAM in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

ADVERSE REACTIONS

ULTRAM was administered to 550 patients during the double-blind or open-label extension periods in U.S. studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 2 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to ULTRAM administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for ULTRAM and the active control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the ULTRAM groups.

Table 2: Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain (N=427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"[1]	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

[1] "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Incidence 1% to less than 5%, possibly causally related: the following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists.

Body as a Whole: Malaise.

Cardiovascular: Vasodilation.

Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.

Gastrointestinal: Abdominal pain, Anorexia, Flatulence.

Musculoskeletal: Hypertonia.

Skin: Rash.

Special Senses: Visual disturbance.

Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Incidence less than 1%, possibly causally related: the following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in post-marketing experience.

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).

Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.

Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see WARNINGS), Tremor.

Respiratory: Dyspnea.

Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.

Special Senses: Dysgeusia.

Urogenital: Dysuria, Menstrual disorder.

Other adverse experiences, causal relationship unknown: A variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials and/or reported in post-marketing experience. A causal relationship between ULTRAM and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.

Central Nervous System: Migraine, Speech disorders.

Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.

Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.

Sensory: Cataracts, Deafness, Tinnitus.

DRUG ABUSE AND DEPENDENCE

ULTRAM may induce psychic and physical dependence of the morphine-type (μ-opioid). (See WARNINGS.) Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. ULTRAM is associated with craving and tolerance development. Withdrawal symptoms may occur if ULTRAM is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with ULTRAM discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical

experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS.) Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with ULTRAM. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with ULTRAM, the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

DOSAGE AND ADMINISTRATION

Adults (17 years of age and over)
For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**
For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day**.

Individualization of Dose

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

- In all patients with **creatinine clearance less than 30 mL/min,** it is recommended that the dosing interval of ULTRAM be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.
- The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.
- In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years old**, total dose should not exceed 300 mg/day.

HOW SUPPLIED

ULTRAM (tramadol hydrochloride tablets) Tablets - 50 mg (white, scored, film-coated capsule-shaped tablet) debossed “ULTRAM” on one side and “06 59” on the other side.

100's NDC 0045-0659-60 bottles of 100 tablets

500's NDC 0045-0659-70 bottles of 500 tablets

Packages of 100 unit doses in blister packs - NDC 0045-0659-10 (10 cards of 10 tablets each).

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F).

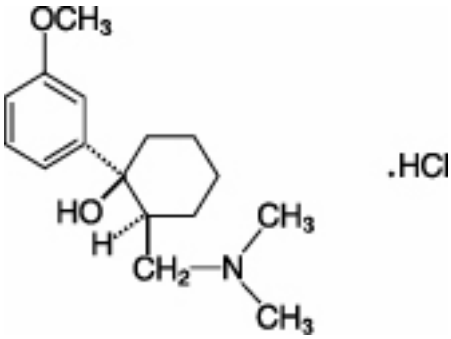
OMP DIVISION
ORTHO-McNEIL
PHARMACEUTICAL, INC.
Raritan, New Jersey 08869
U.S. Patents 3,652,589 and 3,830,934
 Revised MONTH 2003 XXXXXX

ULTRACET™ (tramadol hydrochloride/acetaminophen tablets)

DESCRIPTION

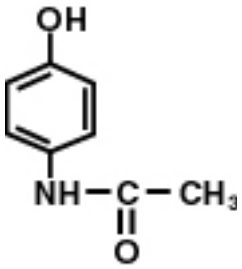
ULTRACET™ (37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets) combines two analgesics, tramadol and acetaminophen.

The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol. It's structural formula is:



The molecular weight of acetaminophen is 151.17. Acetaminophen is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

ULTRACET Tablets contain 37.5 mg tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, OPADRY® Light Yellow, and carnauba wax.

CLINICAL PHARMACOLOGY

The following information is based on studies of tramadol alone or acetaminophen alone, except where otherwise noted:

Pharmacodynamics

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon

the plasma concentrations of each compound (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.

Acetaminophen
Acetaminophen is a non-opiate, non-salicylate analgesic.

Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one ULTRACET tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose Of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		acetaminophen	
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (h)	1.8	(0.6)	1.8	(0.7)	2.1	(0.7)	2.2	(0.7)	0.9	(0.7)
CL/F (mL/min)	588	(226)	736	(244)	-	-	-	-	365	(84)
$t_{1/2}$ (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

[a] For acetaminophen, C_{max} was measured as µg/mL.

A single dose pharmacokinetic study of ULTRACET in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1 and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of ULTRACET, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Absorption:
The absolute bioavailability of tramadol from ULTRACET tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of ULTRAM® tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two ULTRACET tablets occurs at approximately two and three hours, respectively, post-dose.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Oral absorption of acetaminophen following administration of ULTRACET occurs primarily in the small intestine.

Food Effects:
When ULTRACET was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentration or the extent of absorption of either tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.
Distribution:
The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively,

following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range. Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism:
Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see PRECAUTIONS, Drug Interactions).
Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide;

b) conjugation with sulfate; and

c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination:
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of ULTRACET. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of ULTRACET. The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations

Renal:
The pharmacokinetics of ULTRACET in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min, adjustment of dosing regimen in this patient population is recommended. (See DOSAGE AND ADMINISTRATION.) The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.
Hepatic:
The pharmacokinetics and tolerability of ULTRACET in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of ULTRACET in patients with hepatic impairment is not recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).
Geriatric:
A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with ULTRACET which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function (see PRECAUTIONS, Geriatric Use).
Gender:
Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of ULTRACET in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.
Pediatric:
Pharmacokinetics of ULTRACET Tablets have not been studied in pediatric patients below 16 years of age.

Clinical Studies

Single Dose Studies for Treatment of Acute Pain

In pivotal single-dose studies in acute pain, two tablets of ULTRACET administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose. The onset of pain relief after ULTRACET was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after ULTRACET was longer than acetaminophen alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

INDICATIONS AND USAGE

ULTRACET is indicated for the short-term (five days or less) management of acute pain.

CONTRAINDICATIONS

ULTRACET should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids. ULTRACET is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRACET may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Seizure Risk

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS – Use with MAO Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET (see CONTRAINDICATIONS).

Respiratory Depression

Administer ULTRACET cautiously in patients at risk for respiratory depression. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS, Seizure Risk and OVERDOSAGE).

Interaction With Central Nervous System (CNS) Depressants

ULTRACET should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients**.**

Increased Intracranial Pressure or Head Trauma

ULTRACET should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients.

Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRACET (see Respiratory Depression).

Use in Ambulatory Patients

Tramadol may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors

Use ULTRACET with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Use With Alcohol

ULTRACET should not be used concomitantly with alcohol consumption. The use of ULTRACET in patients with liver disease is not recommended.

Use With Other Acetaminophen-containing Products

Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, ULTRACET should not be used concomitantly with other acetaminophen-containing products.

Withdrawal

Withdrawal symptoms may occur if ULTRACET is discontinued abruptly. (See DRUG ABUSE AND DEPENDENCE.) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with ULTRACET discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering ULTRACET at the time of discontinuation.

Physical Dependence and Abuse

Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid). (See DRUG ABUSE AND DEPENDENCE.) Tramadol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence.

Risk of Overdosage

Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. (See OVERDOSAGE.)

Serious potential consequences of overdosage with acetaminophen are hepatic (centrilobular) necrosis, leading to hepatic failure and death. Emergency help should be sought immediately and treatment initiated immediately if overdose is suspected, even if symptoms are not apparent.

PRECAUTIONS

General

The recommended dose of ULTRACET should not be exceeded.

Do not co-administer ULTRACET with other tramadol or acetaminophen-containing products. (See WARNINGS, Use With Other Acetaminophen-containing Products and Risk of Overdosage.)

Pediatric Use

The safety and effectiveness of ULTRACET has not been studied in the pediatric population.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease and multiple drug therapy.

Acute Abdominal Conditions

The administration of ULTRACET may complicate the clinical assessment of patients with acute abdominal conditions**.**

Use in Renal Disease

ULTRACET has not been studied in patients with impaired renal function. Experience with tramadol suggest that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours.

Use in Hepatic Disease

ULTRACET has not been studied in patients with impaired hepatic function. The use of ULTRACET in patients with hepatic impairment is not recommended (see WARNINGS, Use With Alcohol).

Information for Patients

- ULTRACET may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- ULTRACET should not be taken with alcohol containing beverages.
- The patient should be instructed not to take ULTRACET in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations.
- ULTRACET should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see PRECAUTIONS, Labor and Delivery).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, hepatic toxicity and death.

Drug Interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple

oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Use With Carbamazepine
Patients taking **carbamazepine** may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of ULTRACET and carbamazepine is not recommended.

Use With Quinidine
Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.
Use With Inhibitors of CYP2D6
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.
Use With Cimetidine
Concomitant administration of ULTRACET and **cimetidine** has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRACET dosage regimen is recommended.
Use With MAO Inhibitors
Interactions with **MAO Inhibitors**, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use with MAO Inhibitors).
Use With Digoxin
Post-marketing surveillance of tramadol has revealed rare reports of **digoxin** toxicity.
Use With Warfarin Like Compounds
Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.
While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when ULTRACET and warfarin-like compounds are administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.5 times the maximum daily human tramadol dosage of 185 mg/m^2) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 1 time the maximum daily human tramadol dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall,

the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (350 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.6 and 2.4 times the maximum daily human tramadol dosage of 185 mg/m^2.

Pregnancy

Teratogenic Effects: *Pregnancy Category C*
No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m^2 or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m^2), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Non-teratogenic effects:

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 2.6 times the maximum daily human tramadol dosage).

There are no adequate and well-controlled studies in pregnant women. ULTRACET should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported with tramadol hydrochloride during post-marketing.

Labor and Delivery

ULTRACET should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. (See DRUG ABUSE AND DEPENDENCE.) Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRACET, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRACET is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

ADVERSE REACTIONS

Table 2 reports the incidence rate of treatment-emergent adverse events over five days of ULTRACET use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 2: Incidence of Treatment-Emergent Adverse Events (≥2.0%)

Body System Preferred Term	ULTRACET (N=142) (%)
Gastrointestinal System Disorders	
Constipation	6
Diarrhea	3
Nausea	3
Dry Mouth	2
Psychiatric Disorders	
Somnolence	6
Anorexia	3
Insomnia	2
Central & Peripheral Nervous System	
Dizziness	3
Skin and Appendages	
Sweating Increased	4
Pruritus	2
Reproductive Disorders, Male *	
Prostatic Disorder	2

* Number of males = 62

Incidence at least 1%, causal relationship at least possible or greater: the following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of ULTRACET.

Body as a Whole – Asthenia, fatigue, hot flushes
Central and Peripheral Nervous System – Dizziness, headache, tremor
Gastrointestinal System – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting
Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence
Skin and Appendages – Pruritus, rash, increased sweating.

Selected Adverse events occurring at less than 1%: the following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in ULTRACET clinical trials.

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome
Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension
Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo
Gastrointestinal System – Dysphagia, melena, tongue edema
Hearing and Vestibular Disorders – Tinnitus
Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia
Liver and Biliary System – Hepatic function abnormal
Metabolic and Nutritional Disorders – Weight decrease
Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking
Red Blood Cell Disorders – Anemia
Respiratory System – Dyspnea
Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention
Vision Disorders – Abnormal vision
Other clinically significant adverse experiences previously reported with tramadol hydrochloride.
Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial

ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

Other clinically significant adverse experiences previously reported with acetaminophen.
Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

DRUG ABUSE AND DEPENDENCE

Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid). (See WARNINGS.) Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with a prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. Tramadol is associated with craving and tolerance development. Withdrawal symptoms may occur if tramadol is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection and rarely hallucinations. Other symptoms that have been seen less frequently with ULTRACET discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

ULTRACET is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and or seizures. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS.) Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with tramadol.

Acetaminophen

Serious potential consequences of overdosage with acetaminophen are hepatic centrilobular necrosis, leading to hepatic failure and death. Renal tubular necrosis, hypoglycemia and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post ingestion.

Treatment of Overdose

A single or multiple overdose with ULTRACET may be a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

In treating an overdose of ULTRACET, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone

administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Standard recommendations should be followed for the treatment of acetaminophen overdose.

DOSAGE AND ADMINISTRATION

For the short-term (five days or less) management of acute pain, the recommended dose of ULTRACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Individualization of Dose

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours. Dose selection for an elderly patient should be cautious, in view of the potential for greater sensitivity to adverse events.

HOW SUPPLIED

ULTRACET (37.5 mg tramadol hydrochloride/325 mg acetaminophen) Tablets (light yellow, film-coated capsule-shaped tablet) debossed “O-M” on one side and “650” on the other are available as follows:

20’s: NDC 0045 0650 50 (Bottles of 20 tablets)

100’s: NDC 0045 0650 60 (Bottles of 100 tablets)

500’s: NDC 0045 0650 70 (Bottles of 500 tablets)

HUD 100’s: NDC 0045 0650 10 (Packages of 100 unit doses in blister packs, 10 cards of 10 tablets each)

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 - 86°F).

<space allocated for Ortho-McNeil logo>
OMP DIVISION
ORTHO-McNEIL
PHARMACEUTICAL, INC.
Raritan, New Jersey 08869
U.S. Patent 5,336,691 635-11-231-__
 Issued MONTH YEAR XXXXX

Exhibit D

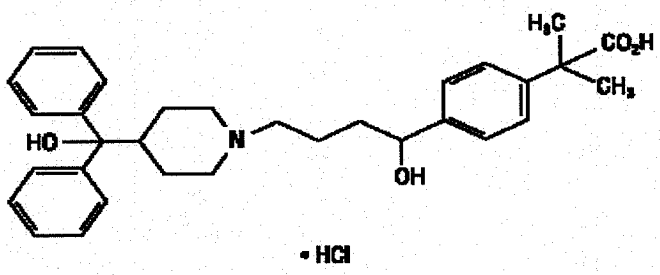
ENCLOSURE 1

Labeling of the Proposed Product –
Fexofenadine Hydrochloride for Oral Suspension
30 mg/5 mL and 60 mg/5 mL

FEXOFENADINE HYDROCHLORIDE FOR ORAL SUSPENSION
30 mg/5 mL and 60 mg/5 mL
Rx only

DESCRIPTION

Fexofenadine hydrochloride, the active ingredient of Fexofenadine Hydrochloride for Oral Suspension, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride. It has the following chemical structure:



The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4$•HCl.
Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.
Inactive ingredients will be furnished when ANDA is submitted, since this is proprietary information. The inactives are GRAS ingredients at appropriate levels.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Both enantiomers of fexofenadine hydrochloride displayed approximately equipotent antihistaminic effects. Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. The clinical significance of these findings is unknown. In laboratory animals, no anticholinergic or alpha$_1$-adrenergic blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

Pharmacokinetics

The pharmacokinetics of fexofenadine hydrochloride in subjects with seasonal allergic rhinitis and subjects with chronic urticaria were similar to those in healthy volunteers.

Absorption:

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single dose of two 60 mg capsule to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours post-dose. After administration of a single 60 mg capsule to healthy volunteers, the mean maximum plasma concentration was 131 ng/mL. Following single dose oral administrations of either the 60 and 180 mg tablet to healthy adult male volunteers, mean maximum plasma concentrations were 142 and 494 ng/mL, respectively. The tablet formulations are bioequivalent to the capsule when administered at

equal doses. Fexofenadine hydrochloride pharmacokinetics are linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily). The administration of the 60 mg capsule contents mixed with applesauce did not have a significant effect on the pharmacokinetics of fexofenadine in adults. Co-administration of 180 mg fexofenadine hydrochloride tablet with a high fat meal decreased the AUC and C_{max} of fexofenadine by 21 and 20% respectively.

Distribution:

Fexofenadine hydrochloride is 60% to 70% bound to plasma proteins, primarily albumin and α_1- acid glycoprotein.

Metabolism:

Approximately 5% of the total dose of fexofenadine hydrochloride was eliminated by hepatic metabolism.

Elimination:

The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg twice daily in healthy volunteers.

Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents primarily unabsorbed drug or the result of biliary excretion.

Special Populations:

Pharmacokinetics in special populations (for renal, hepatic impairment, and age), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those from healthy volunteers in a separate study of similar design.

Geriatric Subjects: In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (<65 years old). Mean fexofenadine elimination half-lives were similar to those observed in younger subjects.

Pediatric Subjects: Cross study comparisons indicated that fexofenadine area under the curve (AUC) following oral administration of a 60 mg dose of fexofenadine hydrochloride to 7-12 year old pediatric subjects with allergic rhinitis was 56% greater compared to healthy adult volunteers given the same dose. Plasma exposure in pediatric subjects given 30 mg fexofenadine hydrochloride is comparable to adults given 60 mg.

Renally Impaired: In subjects with mild to moderate (creatinine clearance 41-80 mL/min) and severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy volunteers. Peak plasma levels in subjects on dialysis (creatinine clearance ≤10 mL/min) were 82% greater and half-life was 31% longer than observed in healthy volunteers. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See **DOSAGE AND ADMINISTRATION**).

Hepatically Impaired: The pharmacokinetics of fexofenadine in subjects with hepatic disease did not differ substantially from that observed in healthy volunteers.

Effect of Gender: Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine hydrochloride.

Pharmacodynamics

Wheal and Flare: Human histamine skin wheal and flare studies following single and twice daily doses of 20 and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2 to 3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing. The clinical significance of these observations is unknown.

Histamine skin wheal and flare studies in 7 to 12 year old subjects showed that following a single dose of 30 or 60 mg, antihistamine effect was observed at 1 hour and reached a maximum by 3 hours. Greater than 49% inhibition of wheal area, and 74% inhibition of flare area were maintained for 8 hours following the 30 and 60 mg dose.

Effects on QT_c: In dogs (30 mg/kg/orally twice daily for 5 days) and rabbits (10 mg/kg, intravenously over 1 hour), fexofenadine hydrochloride did not prolong QT_c. In dogs, the plasma fexofenadine concentration was approximately 9 times the therapeutic plasma concentrations in adults receiving the maximum recommended human daily oral dose of 180 mg. In rabbits, the plasma fexofenadine concentration was approximately 20 times the therapeutic plasma concentration in adults receiving the maximum recommended human daily oral dose of 180 mg. No effect was observed on calcium channel current, delayed K^+ channel current, or action potential duration in guinea pig myocytes, Na^+ current in rat neonatal myocytes, or on the delayed rectifier K^+ channel cloned from human heart at concentrations up to 1 x 10-5 M of fexofenadine.

No statistically significant increase in mean QT_c interval compared to placebo was observed in 714 subjects with seasonal allergic rhinitis given fexofenadine hydrochloride capsules in doses of 60 to 240 mg twice daily for 2 weeks. Pediatric subjects from 2 placebo-controlled trials (n=855) treated with up to 60 mg fexofenadine hydrochloride twice daily demonstrated no significant treatment- or dose-related increases in QT_c. In addition, no statistically significant increase in mean QT_c interval compared to placebo was observed in 40 healthy volunteers given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days, or in 230 healthy volunteers given fexofenadine hydrochloride 240 mg once daily for 1 year. In subjects with chronic idiopathic urticaria, there were no clinically relevant differences for any ECG intervals, including QT_c, between those treated with fexofenadine hydrochloride 180 mg once daily (n = 163) and those treated with placebo (n = 91) for 4 weeks.

Clinical Studies

Seasonal Allergic Rhinitis:

Adults: In three 2-week, multicenter, randomized, double-blind, placebo-controlled trials in subjects 12 to 68 years of age with seasonal allergic rhinitis (n=1634), fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Statistically significant reductions in symptom scores were observed following the first 60 mg dose, with the effect maintained throughout the 12-hour interval. In these studies, there was no additional reduction in total symptom scores with higher doses of fexofenadine hydrochloride up to 240 mg twice daily.

In one 2-week, multicenter, randomized, double-blind clinical trial in subjects 12 to 65 years of age with seasonal allergic rhinitis (n=863), fexofenadine hydrochloride 180 mg once daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Although

the number of subjects in some of the subgroups was small, there were no significant differences in the effect of fexofenadine hydrochloride across subgroups of subjects defined by gender, age, and race. Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60 mg fexofenadine hydrochloride dose administered to subjects with seasonal allergic rhinitis who were exposed to ragweed pollen in an environmental exposure unit. In 1 clinical trial conducted with fexofenadine hydrochloride 60 mg capsules, and in 1 clinical trial conducted with fexofenadine hydrochloride and pseudoephedrine 12 Hour extended release tablets, onset of action was seen within 1 to 3 hours.

Pediatrics: Two 2-week multicenter, randomized, placebo-controlled, double-blind trials in 877 pediatric subjects 6 to 11 years of age with seasonal allergic rhinitis were conducted at doses of 15, 30, and 60 mg twice daily. In 1 of these 2 studies, conducted in 411 pediatric subjects, all 3 doses of fexofenadine hydrochloride significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo, however, a dose-response relationship was not seen. The 60 mg twice daily dose did not provide any additional benefit over the 30 mg twice daily dose. Furthermore, exposure in pediatric subjects given 30 mg fexofenadine hydrochloride is comparable to adults given 60 mg (see **CLINICAL PHARMACOLOGY**).

Three clinical safety studies in 845 children aged 6 months to 5 years with allergic rhinitis comparing 15 mg twice daily (n=85) and 30 mg twice daily (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted. In general, fexofenadine hydrochloride was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See **PRECAUTIONS: Pediatric Use** and **ADVERSE REACTIONS**.)

Chronic Idiopathic Urticaria:

Two 4-week multicenter, randomized, double-blind, placebo-controlled clinical trials compared four different doses of fexofenadine hydrochloride tablet (20, 60, 120, and 240 mg twice daily) to placebo in subjects aged 12 to 70 years with chronic idiopathic urticaria (n=726). Efficacy was demonstrated by a significant reduction in mean pruritus scores (MPS), mean number of wheals (MNW), and mean total symptom scores (MTSS, the sum of the MPS and MNW score). Although all 4 doses were significantly superior to placebo, symptom reduction was greater and efficacy was maintained over the entire 4-week treatment period with fexofenadine hydrochloride doses of ≥60 mg twice daily. However, no additional benefit of the 120 or 240 mg fexofenadine hydrochloride twice daily dose was seen over the 60 mg twice daily dose in reducing symptom scores. There were no significant differences in the effect of fexofenadine hydrochloride across subgroups of subjects defined by gender, age, weight, and race.

In one 4-week, multicenter, randomized, double-blind, placebo-controlled clinical trial in subjects 12 years of age and older with chronic idiopathic urticaria (n=259), fexofenadine hydrochloride 180 mg once daily significantly reduced the mean number of wheals (MNW), the mean pruritus score (MPS), and the mean total symptom score (MTSS, the sum of the MPS and MNW scores). Similar reductions were observed for mean number of wheals and mean pruritus score at the end of the 24-hour dosing interval. Symptom reduction was greater with fexofenadine hydrochloride 180 mg than with placebo. Improvement was demonstrated within 1 day of treatment with fexofenadine hydrochloride 180 mg and was maintained over

the entire 4-week treatment period. There were no significant differences in the effect of fexofenadine hydrochloride across subgroups of subjects defined by gender, age, and race.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis

Fexofenadine hydrochloride for oral suspension is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

Chronic Idiopathic Urticaria

Fexofenadine hydrochloride for oral suspension is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.

CONTRAINDICATIONS

Fexofenadine hydrochloride is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Information for Patients

Patients taking fexofenadine hydrochloride should receive the following information:

Fexofenadine hydrochloride is prescribed for the relief of symptoms of seasonal allergic rhinitis or for the relief of symptoms of chronic idiopathic urticaria (hives). Patients should be instructed to take fexofenadine hydrochloride only as prescribed. Do not exceed the recommended dose. If any untoward effects occur while taking fexofenadine hydrochloride, discontinue use and consult the doctor.

The product should not be used by patients who are hypersensitive to it or to any of its ingredients.

Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.

Patients should be advised to take the tablet with water. Patients should also be advised to store the medication in a tightly closed container in a cool, dry place, away from children.

Drug Interaction with Erythromycin and Ketoconazole

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co–administration of fexofenadine hydrochloride with either ketoconazole or erythromycin led to increased plasma concentrations of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of either erythromycin or ketoconazole. In 2 separate studies, fexofenadine hydrochloride 120 mg twice daily (240 mg total daily dose) was co-administered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy volunteers (n=24, each study). No differences in adverse events or QT_c interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with either erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on steady-state fexofenadine pharmacokinetics after 7 days of co-administration with fexofenadine hydrochloride 120 mg every 12 hours (two times the recommended twice daily dose) in healthy volunteers (n=24)

Concomitant Drug	C_{maxSS} *(Peak plasma concentration)*	$AUC_{ss(0-12h)}$ *(Extent of systemic exposure)*
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro, in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Drug Interactions with Antacids

Administration of 120 mg of fexofenadine hydrochloride (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox®) decreased fexofenadine AUC by 41% and C_{max} by 43%. Fexofenadine hydrochloride should not be taken closely in time with aluminum and magnesium containing antacids.

Interactions with Fruit Juices

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine hydrochloride was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that fexofenadine hydrochloride should be taken with water (see **Dosage and Administration**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine hydrochloride exposure (based on plasma area-under-the-concentration vs. time [AUC] values). No evidence of carcinogenicity was observed in an 18-month study in mice and in a 24-month study in rats at

oral doses up to 150 mg/kg of terfenadine (which led to fexofenadine exposures that were approximately 3 and 5 times the exposure from the maximum recommended human daily oral dose of fexofenadine hydrochloride in adults [180 mg] and children [60 mg], respectively).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

In rat dietary fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at an oral dose of 150 mg/kg of terfenadine (which led to fexofenadine hydrochloride exposures that were approximately 3 times the exposure of the maximum recommended human daily oral dose of 180 mg fexofenadine hydrochloride). In mice, fexofenadine hydrochloride produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 10 times the maximum recommended human daily oral dose of fexofenadine hydrochloride 180 mg based on comparison of AUCs).

Pregnancy

Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral doses of terfenadine up to 300 mg/kg (which led to fexofenadine exposures that were approximately 3 and 30 times, respectively, the exposure from the maximum recommended human daily oral dose of fexofenadine hydrochloride 180 mg based on comparison of AUCs).

In mice, no adverse effects and no teratogenic effects during gestation were observed with fexofenadine at dietary doses up to 3730 mg/kg (approximately 15 times the maximum recommended human daily oral dose of fexofenadine hydrochloride 180 mg based on comparison of AUCs).

There are no adequate and well controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine (approximately 3 times the maximum recommended human daily oral dose of fexofenadine hydrochloride of 180 mg based on comparison of fexofenadine hydrochloride AUCs).

Nursing Mothers

It is not known if fexofenadine is excreted in human milk. There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

The recommended dose in patients 6 to 11 years of age is based on cross-study comparison of the pharmacokinetics of fexofenadine hydrochloride in adults and pediatric subjects and on the safety profile of fexofenadine hydrochloride in both adult and pediatric subjects at doses equal to or higher than the recommended doses.

The safety of fexofenadine hydrochloride at a dose of 30 mg twice daily has been demonstrated in 438 pediatric subjects 6 to 11 years of age in two placebo-controlled 2-week seasonal allergic rhinitis trials. The safety of fexofenadine hydrochloride for the treatment of chronic idiopathic urticaria in subjects 6 to 11 years of age is based on cross-study comparison of the pharmacokinetics of fexofenadine hydrochloride in adult and pediatric

subjects and on the safety profile of fexofenadine in both adult and pediatric subjects at doses equal to or higher than the recommended dose.

The effectiveness of fexofenadine hydrochloride for the treatment of seasonal allergic rhinitis in subjects 6 to 11 years of age was demonstrated in 1 trial (n=411) in which fexofenadine hydrochloride 30 mg twice daily significantly reduced total symptom scores compared to placebo, along with extrapolation of demonstrated efficacy in subjects aged 12 years and above, and the pharmacokinetic comparisons in adults and children. The effectiveness of fexofenadine hydrochloride for the treatment of chronic idiopathic urticaria in patients 6 to 11 years of age is based on an extrapolation of the demonstrated efficacy of fexofenadine hydrochloride in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar in children to that of adult patients.

Three clinical safety studies comparing 15 mg twice daily (n=85) and 30 mg twice daily (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted in pediatric subjects aged 6 months to 5 years. In general, fexofenadine hydrochloride was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See **ADVERSE REACTIONS** and **CLINICAL PHARMACOLOGY**.)

The safety and effectiveness of fexofenadine hydrochloride in pediatric patients under 6 years of age have not been established.

Geriatric Use

Clinical studies of fexofenadine hydrochloride did not include sufficient numbers of subjects aged 65 years and over to determine whether this population responds differently from younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger subjects. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

Seasonal Allergic Rhinitis

Adults: In placebo-controlled seasonal allergic rhinitis clinical trials in subjects 12 years of age and older, which included 2461 subjects receiving fexofenadine hydrochloride capsules at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride- and placebo-treated subjects. All adverse events that were reported by greater than 1% of subjects who received the recommended daily dose of fexofenadine hydrochloride (60 mg capsules twice daily), and that were more common with fexofenadine hydrochloride than placebo, are listed in Table 1.

In a placebo-controlled clinical study in the United States, which included 570 subjects aged 12 years and older receiving fexofenadine hydrochloride tablets at doses of 120 or 180 mg once daily, adverse events were similar in fexofenadine hydrochloride- and placebo-treated subjects. Table 1 also lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at doses of 180 mg once daily and that were more common with fexofenadine hydrochloride than placebo.

The incidence of adverse events, including drowsiness, was not dose-related and was similar across subgroups defined by age, gender, and race.

Table 1
Adverse experiences in subjects aged 12 years and older reported in placebo-controlled seasonal allergic rhinitis clinical trials in the United States

Twice-daily dosing with fexofenadine capsules at rates of greater than 1%

Adverse experience	*Fexofenadine 60 mg Twice Daily (n=679)*	*Placebo Twice Daily (n=671)*
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Once-daily dosing with fexofenadine hydrochloride tablets at rates of greater than 2%

Adverse experience	*Fexofenadine 180 mg Once Daily (n=283)*	*Placebo (n=293)*
Headache	10.6%	7.5%
Upper Respiratory Tract Injection	3.2%	3.1%
Back Pain	2.8%	1.4%

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride- and placebo-treated subjects.

Pediatrics: Table 2 lists adverse experiences in subjects aged 6 to 11 years of age which were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at a dose of 30 mg twice daily in placebo-controlled seasonal allergic rhinitis studies in the United States and Canada that were more common with fexofenadine hydrochloride than placebo.

Table 2
Adverse experiences reported in placebo-controlled seasonal allergic rhinitis studies in pediatric subjects aged 6 to 11 in the United States and Canada at rates of greater than 2%

Adverse experience	Fexofenadine 30 mg *Twice Daily (n=209)*	Placebo *(n=229)*
Headache	7.2%	6.6%
Accidental Injury	2.9%	1.3%
Coughing	3.8%	1.3%
Fever	2.4%	0.9%
Pain	2.4%	0.4%
Otitis Media	2.4%	0.0%
Upper Respiratory Tract Infection	4.3%	1.7%

Three clinical safety studies in 845 children aged 6 months to 5 years comparing 15 mg twice daily (n=85) and 30 mg twice daily (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted. In general, fexofenadine hydrochloride was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See **PRECAUTIONS: Pediatric Use.**)

Chronic Idiopathic Urticaria

Adverse events reported by subjects 12 years of age and older in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies. In placebo-controlled chronic idiopathic urticaria clinical trials, which included 726 subjects 12 years of age and older receiving fexofenadine hydrochloride tablets at doses of 20 to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride- and placebo-treated patients. Table 3 lists adverse experiences in subjects aged 12 years and older which were reported by greater than 2% of subjects treated with fexofenadine hydrochloride 60 mg tablets twice daily in controlled clinical studies in the United States and Canada and that were more common with fexofenadine hydrochloride than placebo.

In a placebo-controlled clinical study in the United States, which included 167 subjects aged 12 years and older receiving fexofenadine hydrochloride 180 mg tablets, adverse events were similar in fexofenadine hydrochloride- and placebo-treated subjects. Table 3 also lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at doses of 180 mg once daily and that were more common with fexofenadine hydrochloride than placebo.

The safety of fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria in pediatric patients 6 to 11 years of age is based on the safety profile of fexofenadine hydrochloride in adults and adolescent patients at doses equal to or higher than the recommended dose (see **Pediatric Use**).

Table 3
Adverse experiences reported in subjects 12 years of age and older in placebo-controlled chronic idiopathic urticaria studies

Twice-daily dosing with fexofenadine hydrochloride in studies in the United States and Canada at rates of greater than 2%

Adverse experience	Fexofenadine 180 mg *Twice Daily* *(n=191)*	Placebo *(n=183)*
Dyspepsia	4.7%	4.4%
Myalgia	2.6%	2.2%
Back Pain	2.1%	1.1%
Dizziness	2.1%	1.1%
Pain in extremity	2.1%	0.0%

Once-daily dosing with fexofenadine hydrochloride in a study in the United States at rates of greater than 2%

Adverse experience	Fexofenadine 180 mg *Twice Daily* *(n=167)*	Placebo *(n=92)*
Headache	4.8%	3.3%
Nasopharyngitis	2.4%	2.2%
Upper Respiratory Tract Infection	2.4%	2.2%

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria subjects with incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

OVERDOSAGE

Reports of fexofenadine hydrochloride overdose have been infrequent and contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg (6 healthy volunteers at this dose level), and doses up to 690 mg twice daily for 1 month (3 healthy volunteers at this dose level) or 240 mg once daily for 1 year (234 healthy volunteers at this dose level) were administered without the development of clinically significant adverse events as compared to placebo.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended. Following administration of terfenadine, hemodialysis did not effectively remove fexofenadine, the major active metabolite of terfenadine, from blood (up to 1.7% removed).

No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (110 times the maximum recommended human daily oral dose in adults and 200 times the maximum recommended human daily oral dose in children based on mg/m²) and up to 5000 mg/kg in rats (230 times the maximum recommended human daily oral dose in adults and 400 times the maximum recommended human daily oral dose in children based on mg/m²). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (300 times the maximum recommended human daily oral dose in adults and 530 times the maximum recommended human daily oral dose in children based on mg/m²).

DOSAGE AND ADMINISTRATION

Strength	Indication	Children 6 to 11 Years♣	Children 12 years & older and Adults♦
30 mg/5 mL	Seasonal Allergic Rhinitis	30 mg twice daily equivalent to 1 tsp twice daily	60 mg twice daily equivalent to 2 tsp twice daily
			180 mg once daily equivalent to 6 tsp once daily
	Chronic Idiopathic Urticaria	30 mg twice daily equivalent to 1 tsp twice daily	60 mg twice daily equivalent to 2 tsp twice daily
			180 mg once daily equivalent to 6 tsp once daily
60 mg/5 mL	Seasonal Allergic Rhinitis	30 mg twice daily equivalent to 1/2 tsp twice daily	60 mg twice daily equivalent to 1 tsp twice daily
			180 mg once daily equivalent to 3 tsp once daily
	Chronic Idiopathic Urticaria	30 mg twice daily equivalent to 1/2 tsp twice daily	60 mg twice daily equivalent to 1 tsp twice daily
			180 mg once daily equivalent to 3 tsp once daily

♣ - A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see **CLINICAL PHARMACOLOGY**).

♦ - A dose of 60 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see **CLINICAL PHARMACOLOGY**).

DIRECTIONS FOR RECONSTITUTION

Reconstitution directions based on the pack sizes will be submitted later in the ANDA.

After reconstitution the suspension may be kept for 30 days at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep tightly closed. Shake well before using. Discard unused portion after 30 days.

HOW SUPPLIED
Package sizes to be determined.

Store dry powder and reconstituted suspension at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].
Keep tightly closed.

Manufactured for:
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